```
=> fil medl drugu capl biosis embase wpids; d que l4; d que l6
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FILE 'DRUGU' ENTERED AT 15:03:30 ON 10 DEC 2004
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L1           181 SEA KNEGTEL R?/AU
L2           100 SEA MORTIMORE M?/AU
L3           121 SEA STUDLEY J?/AU
L4             5 SEA L1 AND L2 AND L3



L1           181 SEA KNEGTEL R?/AU
L2           100 SEA MORTIMORE M?/AU
L3           121 SEA STUDLEY J?/AU
L5         20870 SEA CASPASE#(3A)(INHIB? OR BLOCK? OR ANTAG?)
L6            19 SEA (L1 OR L2 OR L3) AND L5


=> s l4 or l6
L7            19 L4 OR L6

=> dup rem l7
PROCESSING COMPLETED FOR L7
L8            11 DUP REM L7 (8 DUPLICATES REMOVED)
                 ANSWERS '1-9' FROM FILE CAPLUS
                 ANSWER '10' FROM FILE BIOSIS
                 ANSWER '11' FROM FILE WPIDS

=> d ibib ed ab hitind 1-9; d iall 10-11

L8   ANSWER 1 OF 11  CAPLUS  COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2004:565214  CAPLUS
DOCUMENT NUMBER:          141:106388
TITLE:                    Preparation of 4-oxo-3-(1-oxo-1H-isoquinolin-2-
                          ylacetylamino)-pentanoic acid ester and amide
                          derivatives as caspase inhibitors
INVENTOR(S):              Charrier, Jean-Damien; Mortimore, Michael;
                          Studley, John R.
PATENT ASSIGNEE(S):       Vertex Pharmaceuticals Incorporated, USA
SOURCE:                   PCT Int. Appl., 104 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:
```

inventors

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004058718	A1	20040715	WO 2003-US40870	20031222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004192612	A1	20040930	US 2003-743563	20031222
PRIORITY APPLN. INFO.:			US 2002-435133P P	20021220

OTHER SOURCE(S): MARPAT 141:106388

ED Entered STN: 15 Jul 2004

AB The title compds. of formula I [X = alkoxy, (substituted) NH2, etc.; Y = halo, trifluorophenoxy, tetrafluorophenoxy; R1 = alkyl; R2, R3 = H, halo, OCF3, CN, CF3] are prepared The present invention also provides pharmaceutical compns. and methods using such compns. for treating a caspase-mediated disease, particularly in the central nervous system. Thus, II was prepared from 7-chloroisochromen-1-one (preparation given), (S)-2-aminobutyric acid tert-Bu ester and 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester.

IC ICM C07D217-24
ICS A61K031-472; A61K031-4725; C07D401-12; C07D405-12; C07D417-12

CC 27-17 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 63

ST isoquinolinylacetylamine oxopentanoic ester amide prepn **caspase inhibitor**

IT Hepatitis
(B; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Hepatitis
(C; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Intestine, disease
(Crohn's; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Nervous system, disease
(Huntington's chorea; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Sarcoma
(Kaposi's; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Spinal muscular atrophy
(X-linked spinal and bulbar muscular atrophy; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Leukemia
(acute myelogenous; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Respiratory distress syndrome
(adult; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Nervous system, disease
(amyotrophic lateral sclerosis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase**

inhibitors)
IT Dermatitis
(atopic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Stomach, disease
(autoimmune gastritis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Anemia (disease)
(autoimmune hemolytic anemia; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Thyroid gland, disease
(autoimmune thyroiditis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Dysentery
(bacillary; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Leukemia
(chronic myelocytic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Artery
(coronary, bypass surgery; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Disease, animal
(degenerative; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Infection
(dengue; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Platelet (blood)
(disease, thrombocytopenia; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Intestine, disease
(duodenum, ulcer; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Heart, disease
(failure; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Kidney, disease
(glomerulonephritis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Transplant and Transplantation
(graft-vs.-host reaction; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Anemia (disease)
(hemolytic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Shock (circulatory collapse)
(hemorrhagic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Heart, disease
(infarction; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Intestine, disease
(inflammatory; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic

acid ester and amide derivs. as **caspase inhibitors**)
IT Spinal cord, disease
(injury; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Diabetes mellitus
(insulin-dependent; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Brain, disease
Heart, disease
(ischemia; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Melanoma
(metastatic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Agranulocytosis
(neutropenia; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Pancreas, disease
(pancreatitis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Peritoneum, disease
(peritonitis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT Kidney, disease
(polycystic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT AIDS (disease)
Aging, animal
Alcoholism
Alopecia
Alzheimer's disease
Apoptosis
Asthma
Atherosclerosis
Autoimmune disease
Bone, disease
Burn
Cell death
Diabetes mellitus
Drug delivery systems
Encephalitis
Epilepsy
Graves' disease
Heart, disease
Hepatitis GB virus C/G
Human
Immunotherapy
Infection
Inflammation
Japanese encephalitis virus
Kidney, disease
Leukemia
Liver, disease
Meningitis
Multiple myeloma
Multiple sclerosis
Myasthenia gravis
Myelodysplastic syndromes
Neoplasm
Nervous system agents
Osteoarthritis

Osteoporosis
Parkinson's disease
Prion diseases
Psoriasis
Rheumatoid arthritis
Sepsis
Spinal muscular atrophy
Transplant rejection
Tuberculosis
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Interleukin 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Drug delivery systems
(prodrugs; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Disease, animal
(proliferative; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Eye, disease
(retinopathy; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Skin, disease
(scar; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Connective tissue, disease
(scleroderma; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Shock (circulatory collapse)
(septic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Lupus erythematosus
(systemic; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Brain, disease
(trauma; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Stomach, disease
(ulcer; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Intestine, disease
(ulcerative colitis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Eye, disease
(uveitis; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Hepatitis
(viral, chronic active; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Infection
(viral; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT Fever and Hyperthermia
(yellow; preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

IT 186322-81-6, Caspase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and

amide derivs. as **caspase inhibitors**)
IT 640286-59-5P 721397-83-7P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT 721397-79-1P 721397-80-4P 721397-81-5P 721397-82-6P 721397-84-8P
721397-85-9P 721397-86-0P 721397-87-1P 721397-88-2P 721397-89-3P
721397-90-6P 721397-91-7P 721397-92-8P 721397-93-9P 721397-94-0P
721397-95-1P 721397-96-2P 721397-97-3P 721397-98-4P 721397-99-5P
721398-00-1P 721398-01-2P 721398-02-3P 721398-03-4P 721398-04-5P
721398-05-6P 721398-06-7P 721398-07-8P 721398-08-9P 721398-09-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT 122-01-0, 4-Chlorobenzoyl chloride 769-39-1, 2,3,5,6-Tetrafluorophenol 942-06-3, 4,5-Dichlorophthalic anhydride 4009-98-7, Methoxymethyltriphenylphosphonium chloride 4506-45-0 23984-83-0 75190-94-2 147221-33-8 153088-76-7 161401-79-2, 3-Amino-5-fluoro-4-hydroxypentanoic acid tert-butyl ester 385438-94-8 640286-67-5 640286-68-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)
IT 4657-56-1P 6873-44-5P 24006-91-5P 124033-36-9P 124033-37-0P
131001-98-4P 254750-84-0P 254751-09-2P 618459-84-0P 640286-42-6P
640286-55-1P 640286-56-2P 640286-57-3P 640286-58-4P 640286-60-8P
721398-10-3P 721398-11-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as **caspase inhibitors**)

L8 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:20662 CAPLUS
DOCUMENT NUMBER: 140:77410
TITLE: Preparation of isoquinolinone and quinazolinone peptide derivatives as **caspase inhibitors**
INVENTOR(S): **Knegtel, Ronald**; **Mortimore, Michael**; **Studley, John**; Millan, David
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004002961	A1	20040108	WO 2003-US20557	20030627

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,

KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2004072850 A1 20040415 US 2003-609147 20030627
PRIORITY APPLN. INFO.: US 2002-392592P P 20020628
US 2002-435073P P 20021220

OTHER SOURCE(S): MARPAT 140:77410
ED Entered STN: 11 Jan 2004
AB The invention relates to isoquinolinones and quinazolinones I [X is CH or N; Y is halo, tri- or tetrafluorophenoxy; R2 is alkyl; R3 is H, halo, OCF3, CN, or CF3; R4 is groups R3 or alkylthio, (un)substituted Ph, phenoxy, or phenylthio; with the proviso that when Y is halo, then R3 and R4 are not both H] which are caspase inhibitors useful in compns. for the treatment of various diseases, conditions, or disorders. Thus, I (X = CH, Y = F, R2 = Et, R3 = H, R4 = Cl), prepared by coupling of (S)-2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)butyric acid (preparation given) with 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester, had Ki (M-1 s-1) > 500,000 for inhibition of caspase-1 or caspase-3, Ki 100,000-500,000 for inhibition of caspase-8, and IC50 < 1 μM for inhibition of interleukin-1β secretion.
IC ICM C07D217-24
ICS C07D239-90; A61K031-472; A61K031-517
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7, 27, 28, 63
ST peptide deriv isoquinolinone quinazolinone prepn **inhibitor caspase**
IT Hepatitis
(B; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Hepatitis
(C; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Intestine, disease
(Crohn's; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Stomach, disease
(H. pylori-associated; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Human immunodeficiency virus
(HIV-related encephalitis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Nervous system, disease
(Huntington's chorea; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Sarcoma
(Kaposi's; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Spinal muscular atrophy
(X-linked spinal and bulbar muscular atrophy; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Leukemia
(acute myelogenous; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Respiratory distress syndrome
(adult; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Nervous system, disease
(amyotrophic lateral sclerosis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Antiarteriosclerotics

(antiatherosclerotics; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Dermatitis
(atopic; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Stomach, disease
(autoimmune gastritis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Anemia (disease)
(autoimmune hemolytic anemia; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Thyroid gland, disease
(autoimmune thyroiditis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Leukemia
(chronic myelocytic; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Artery
(coronary, bypass surgery; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Disease, animal
(degenerative; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Infection
(dengue; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Platelet (blood)
(disease, thrombocytopenia; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Intestine, disease
(duodenum, ulcer, H. pylori-associated; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Heart, disease
Organ, animal, disease
(failure; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Helicobacter pylori
(gastric and duodenal ulcer disease; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Kidney, disease
(glomerulonephritis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Transplant and Transplantation
(graft-vs.-host reaction; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Shock (circulatory collapse)
(hemorrhagic; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Heart, disease
(infarction; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Intestine, disease
(inflammatory; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Spinal cord, disease
(injury; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Brain, disease
Heart, disease

(ischemia; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Melanoma
(metastatic; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Agranulocytosis
(neutropenia, autoimmune; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Pancreas, disease
(pancreatitis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Peritoneum, disease
(peritonitis, inflammatory; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Kidney, disease
(polycystic; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)
IT Aging, animal
Alcoholism
Alopecia
Alzheimer's disease
Anti-Alzheimer's agents
Anti-infective agents
Anti-inflammatory agents
Antiarthritics
Antiasthmatics
Anticonvulsants
Antidiabetic agents
Antirheumatic agents
Antitumor agents
Antiviral agents
Apoptosis
Asthma
Atherosclerosis
Autoimmune disease
Bone, disease
Burn
Cell death
Diabetes mellitus
Encephalitis
Epilepsy
Graves' disease
Heart, disease
Immunotherapy
Infection
Inflammation
Kidney, disease
Leukemia
Liver, disease
Meningitis
Multiple myeloma
Multiple sclerosis
Myasthenia gravis
Myelodysplastic syndromes
Neoplasm
Nervous system, disease
Osteoarthritis
Osteoporosis
Parkinson's disease
Prion diseases
Psoriasis
Rheumatoid arthritis

Sepsis
Spinal muscular atrophy
Tuberculosis
Tuberculostatics
(preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Interleukin 1β
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Disease, animal
(proliferative; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Transplant and Transplantation
(rejection; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Eye, disease
(retinopathy; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Skin, disease
(scar; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Connective tissue, disease
(scleroderma; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Shock (circulatory collapse)
(septic; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Shigella
(shigellosis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Brain, disease
(stroke; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Lupus erythematosus
(systemic; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Brain, disease
(trauma; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Intestine, disease
(ulcerative colitis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Eye, disease
(uveitis; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Hepatitis
(viral, chronic active; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Infection
(viral; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT Fever and Hyperthermia
(yellow; preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT 122191-40-6, Caspase-1 169592-56-7, Caspase-3 179241-78-2, Caspase-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT 618459-84-0P 618459-91-9P 618459-92-0P 618459-97-5P 618459-98-6P
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640286-45-9P 640286-46-0P 640286-47-1P 640286-48-2P 640286-49-3P
640286-50-6P 640286-51-7P 640286-52-8P 640286-53-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT 93-61-8, n Methylformanilide 95-57-8, 2 Chlorophenol 98-80-6, Phenylboronic acid 107-03-9, 1 Propanethiol 122-01-0, 4 Chlorobenzoyl chloride 149-73-5, Trimethyl orthoformate 769-39-1, 2 3 5 6 Tetrafluorophenol 942-06-3, 4 5 Dichlorophthalic anhydride 2516-95-2 4009-98-7, Methoxymethyltriphenylphosphonium chloride 4506-45-0 51282-49-6 53956-05-1 75190-94-2 161401-79-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

IT 6873-44-5P 23984-83-0P 24006-91-5P 59003-74-6P 70097-46-0P 124033-36-9P 124033-37-0P 131001-98-4P 254750-84-0P 254751-09-2P 254751-10-5P 344461-44-5P 640286-54-0P 640286-55-1P 640286-56-2P 640286-57-3P 640286-58-4P 640286-59-5P 640286-60-8P 640286-61-9P 640286-62-0P 640286-63-1P 640286-64-2P 640286-66-4P 640286-67-5P 640286-68-6P 640286-69-7P 640286-70-0P 640286-71-1P 640286-72-2P 640286-73-3P 640286-74-4P 640286-75-5P 640286-76-6P 640286-77-7P 640286-78-8P 640286-79-9P 640286-80-2P 640286-81-3P 640289-04-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of isoquinolinone and quinazolinone peptide derivs. as **caspase inhibitors**)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:656594 CAPLUS
DOCUMENT NUMBER: 139:191460
TITLE: Phospholipids as **caspase inhibitor** prodrugs
INVENTOR(S): **Mortimore, Michael**; Golec, Julian M. C.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 256 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068242	A1	20030821	WO 2003-US4457	20030211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004019017	A1	20040129	US 2003-366192	20030211
PRIORITY APPLN. INFO.:			US 2002-355889P P	20020211

OTHER SOURCE(S): MARPAT 139:191460
ED Entered STN: 22 Aug 2003
AB The invention relates to compds. which are prodrugs of caspase inhibitors and pharmaceutically acceptable salts thereof. The invention further relates to the release of caspase inhibitors from these compds. through selective bond cleavage. The invention further relates to pharmaceutical compns. comprising these compds., which are particularly well-suited for treatment of caspase-mediated diseases, including inflammatory and degenerative diseases. The invention further relates to methods for preparing compds. of this invention.
IC ICM A61K031-685
ICS C07D209-94; C07D209-86; C07D239-90; C07D209-26; C07D211-34; C07D417-06; C07D409-06; C07D271-06; C07D413-12; C07D471-04; A61P037-06; C07C237-36; C07C237-40; C07K005-06; C07F009-10; C07K005-02
CC 1-11 (Pharmacology)
Section cross-reference(s): 63
ST phospholipid **caspase inhibitor** prodrug inflammation degeneration disease therapy
IT Drugs
Preservatives
(blood preservatives; phospholipids as **caspase inhibitor** prodrugs)
IT Artery
(coronary, bypass surgery, complications; phospholipids as **caspase inhibitor** prodrugs)
IT Disease, animal
(degenerative; phospholipids as **caspase inhibitor** prodrugs)
IT Autoimmune disease
Human
Immunotherapy
Inflammation
Thrombolytics
Transplant and Transplantation
(phospholipids as **caspase inhibitor** prodrugs)
IT Interleukin 18
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(phospholipids as **caspase inhibitor** prodrugs)
IT Phospholipids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phospholipids as **caspase inhibitor** prodrugs)
IT Drug delivery systems
(prodrugs; phospholipids as **caspase inhibitor** prodrugs)
IT Interferons
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(γ; phospholipids as **caspase inhibitor** prodrugs)
IT 186322-81-6, **Caspase**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**inhibitors**; phospholipids as **caspase inhibitor** prodrugs)
IT 363154-80-7
RL: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(phospholipids as **caspase inhibitor** prodrugs)
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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phospholipids as **caspase inhibitor** prodrugs)

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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phospholipids as **caspase inhibitor** prodrugs)

IT 294859-64-6 294859-66-8 294859-70-4 294859-72-6 294859-74-8
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RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phospholipids as **caspase inhibitor** prodrugs)

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582316-31-2 582316-32-3 582316-33-4 582316-34-5 582316-35-6
582316-36-7 582316-37-8 582316-38-9 582316-39-0 582316-40-3
582316-41-4 582316-42-5 582316-43-6 582316-44-7 582316-45-8
582316-46-9 582316-47-0 582316-48-1 582316-49-2 582316-50-5
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582316-71-0 582316-72-1 582316-73-2 582316-74-3 582316-75-4
582316-76-5 582316-77-6 582316-78-7 582316-79-8 582316-80-1
582316-81-2 582316-82-3 582316-83-4 582316-84-5 582316-85-6
582316-86-7 582316-87-8 582316-88-9 582316-89-0 582316-90-3
582316-91-4 582316-92-5 582316-93-6 582316-94-7 582316-95-8
582316-96-9 582316-97-0 582316-98-1 582316-99-2 582317-00-8

582317-01-9 582317-02-0 582317-03-1 582317-04-2 582317-05-3
582317-06-4 582317-07-5 582317-08-6 582317-09-7 582317-10-0
582317-11-1 582317-12-2 582317-13-3 582317-14-4 582317-15-5
582317-16-6 582317-17-7 582317-18-8 582317-19-9 582317-20-2
582317-21-3 582317-22-4 582317-23-5 582317-24-6 582317-25-7
582317-26-8 582317-27-9 582317-28-0 582317-29-1 582317-30-4
582317-31-5 582317-32-6 582317-33-7 582317-34-8 582317-35-9
582317-36-0 582317-37-1 582317-38-2 582317-39-3 582317-40-6
582317-41-7 582317-42-8 582317-43-9 582317-44-0 582317-45-1
582317-46-2 582317-47-3
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phospholipids as **caspase inhibitor** prodrugs)

IT 582317-48-4 582317-49-5 582317-50-8 582317-51-9 582317-52-0
582317-53-1 582317-54-2 582317-55-3 582317-56-4 582317-57-5
582317-58-6 582317-59-7 582317-60-0 582317-61-1 582317-62-2
582317-63-3 582317-64-4 582317-65-5 582317-66-6 582317-67-7
582317-68-8 582317-69-9 582317-70-2 582317-71-3 582317-72-4
582317-73-5 582317-74-6 582317-75-7 582317-76-8 582317-77-9
582317-78-0 582317-79-1 582317-80-4 582317-81-5 582317-82-6
582317-83-7 582317-84-8 582317-85-9 582317-86-0 582317-87-1
582317-88-2 582317-89-3 582317-91-7 582317-92-8 582317-93-9
582317-94-0 582317-95-1 582317-96-2 582317-97-3 582317-98-4
582317-99-5 582318-00-1 582318-01-2 582318-02-3 582318-03-4
582318-04-5 582318-05-6 582318-06-7 582318-07-8 582318-08-9
582318-09-0 582318-10-3 582318-11-4 582318-12-5 582318-13-6
582318-14-7 582318-15-8 582318-16-9 582318-17-0 582318-18-1
582318-19-2 582318-20-5 582318-22-7 582318-23-8 582318-24-9
582318-25-0 582318-26-1 582318-27-2 582318-28-3 582318-29-4
582318-30-7 582318-31-8 582318-32-9 582318-33-0 582318-34-1
582318-35-2 582318-36-3 582318-37-4 582318-38-5 582318-39-6
582318-40-9 582318-41-0 582318-42-1 582318-43-2 582318-44-3
582318-45-4 582318-46-5 582318-47-6 582318-48-7 582318-49-8
582318-50-1 582318-51-2 582318-52-3 582318-53-4 582318-54-5
582318-55-6 582318-56-7 582318-57-8 582318-58-9 582318-59-0
582318-60-3 582318-61-4 582318-62-5 582318-74-9 582318-75-0
582318-76-1 582318-77-2 582318-78-3 582318-79-4 582318-80-7
582318-81-8 582318-82-9 582318-83-0 582318-84-1 582318-85-2
582318-86-3 582318-87-4 582321-20-8 582321-21-9 582321-22-0
582321-23-1 582321-24-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phospholipids as **caspase inhibitor** prodrugs)

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2003:396847 CAPLUS
DOCUMENT NUMBER: 138:369193
TITLE: Process for synthesizing aspartic and glutamic acid derivatives especially useful as intermediates in the manufacture of a **caspase inhibitor**
INVENTOR(S): **Mortimore, Michael**; Philps, Oliver; **Studley, John**
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 80 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2003042169	A2	20030522	WO 2002-US32218		20021008
WO 2003042169	A3	20040401			

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1436248	A2	20040714	EP 2002-782135		20021008

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK

US 2003162993	A1	20030828	US 2002-268440		20021009
PRIORITY APPLN. INFO.:			US 2001-328065P	P	20011009
			WO 2002-US32218	W	20021008

OTHER SOURCE(S): CASREACT 138:369193; MARPAT 138:369193

ED Entered STN: 23 May 2003

AB The invention relates to novel diazo ketone derivs. R1NHCH[(CH2)nCO:CHN2](CH2)pCRxRyCH2R5 [R1 is H, an amine-protecting group, or a P2-P4 moiety (or portion) of a caspase inhibitor; Rx is H; Ry is OH or protected alc.; or CRxRy is O(CH2)2-3O or :O (for R1 ≠ H); R5 is an electroneg. leaving group, halo, OH or SH or derivative; n, p = 0-6] and to processes for homologation of these diazo ketone derivs. to compds. that are caspase inhibitors. Thus, (S,S)-CbzNHCH(COCH:N2)CH(OTBDMS)CH2F (Cbz = benzyloxycarbonyl, TBDMS = tert-butyldimethylsilyl) was prepared from (S,S)-4-fluorothreonine via N-protection, silylation, and reaction with diazomethane. The product was converted into the tert-Bu ester and N-deprotected.

IC ICM C07C245-00

CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 7

ST aspartic glutamic acid intermediate **caspase inhibitor**; fluorothreonine diazo ketone deriv prepn; threonine fluoro diazo ketone deriv prepn

IT 186322-81-6, Caspase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(process for synthesizing aspartic and glutamic acid derivs. as intermediates in manufacture of **caspase inhibitor**)

IT 334-88-3, Diazomethane 18107-18-1, Trimethylsilyldiazomethane 75315-63-8 89426-34-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(process for synthesizing aspartic and glutamic acid derivs. as intermediates in manufacture of **caspase inhibitor**)

IT 56-84-8DP, L-Aspartic acid, derivs. 56-86-0DP, L-Glutamic acid, derivs. 89426-52-8P 521970-95-6P 521970-96-7P 521970-97-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(process for synthesizing aspartic and glutamic acid derivs. as intermediates in manufacture of **caspase inhibitor**)

IT 521970-98-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(process for synthesizing aspartic and glutamic acid derivs. as intermediates in manufacture of **caspase inhibitor**)

L8 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2002:905855 CAPLUS
DOCUMENT NUMBER: 138:303

TITLE: **Caspase inhibitors** and therapeutic uses
INVENTOR(S): **Mortimore, Michael**; Miller, Andrew; **Studley, John**; Charrier, Jean-Damien
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002094263	A2	20021128	WO 2002-US16353	20020523
WO 2002094263	A3	20030327		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003092703	A1	20030515	US 2002-153971	20020523
EP 1392289	A2	20040303	EP 2002-729301	20020523
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004531558	T2	20041014	JP 2002-590980	20020523

PRIORITY APPLN. INFO.: US 2001-292969P P 20010523
WO 2002-US16353 W 20020523

OTHER SOURCE(S): MARPAT 138:303
ED Entered STN: 29 Nov 2002
AB This invention provides compds. which are effective inhibitors of apoptosis and IL-1β secretion. The invention also discusses the therapeutic potential of these compds. in treating diseases like IL-1 mediated disease, apoptosis mediated disease or an inflammatory disease.
IC ICM A61K031-4015
ICS A61K031-403; A61K031-407; A61K031-435; A61K031-45; A61K031-498; A61K031-5025; A61K031-538; A61K031-54; A61K031-55; A61P001-00; A61P003-00; A61P007-00; A61P009-00; A61P011-00; A61P013-00; A61P017-00; A61P019-00; A61P021-00; A61P025-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 27
ST **caspase inhibitor** therapeutic IL1 apoptosis cancer inflammation disease
IT Hepatitis
(B; **caspase inhibitors**)
IT Hepatitis
(C; **caspase inhibitors**)
IT Intestine, disease
(Crohn's; **caspase inhibitors**)
IT Hepatitis
(G; **caspase inhibitors**)
IT Encephalitis
(HIV-related; **caspase inhibitors**)
IT Nervous system, disease
(Huntington's chorea; **caspase inhibitors**)
IT Sarcoma
(Kaposi's; **caspase inhibitors**)

IT Spinal muscular atrophy
(X-linked spinal and bulbar muscular atrophy; **caspase inhibitors**)
IT Heart, disease
(acute and chronic; **caspase inhibitors**)
IT Leukemia
(acute myelogenous; **caspase inhibitors**)
IT Respiratory distress syndrome
(adult; **caspase inhibitors**)
IT Hepatitis
(alc.; **caspase inhibitors**)
IT Nervous system, disease
(amyotrophic lateral sclerosis; **caspase inhibitors**)
IT Dermatitis
(atopic; **caspase inhibitors**)
IT Stomach, disease
(autoimmune gastritis; **caspase inhibitors**)
IT Anemia (disease)
(autoimmune hemolytic anemia; **caspase inhibitors**)
IT Thyroid gland, disease
(autoimmune; **caspase inhibitors**)
IT Drugs
Preservatives
(blood preservatives; **caspase inhibitors**)
IT AIDS (disease)
Aging, animal
Alopecia
Alzheimer's disease
Apoptosis
Asthma
Atherosclerosis
Autoimmune disease
Blood preservation
Burn
Diabetes mellitus
Epilepsy
Graves' disease
Human
Immunotherapy
Leukemia
Liver, disease
Meningitis
Multiple myeloma
Multiple sclerosis
Myasthenia gravis
Myelodysplastic syndromes
Neoplasm
Organ preservation
Osteoarthritis
Osteoporosis
Parkinson's disease
Prion diseases
Psoriasis
Rheumatoid arthritis
Sepsis
Spinal muscular atrophy
Tuberculosis
(**caspase inhibitors**)
IT Interleukin 1
Interleukin 1β
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**caspase inhibitors**)

IT Leukemia
(chronic myelocytic; **caspase inhibitors**)
IT Artery
(coronary, bypass surgery; **caspase inhibitors**)
IT Disease, animal
(degenerative; **caspase inhibitors**)
IT Infection
(dengue; **caspase inhibitors**)
IT Bone, disease
(destructive; **caspase inhibitors**)
IT Platelet (blood)
(disease, thrombocytopenia; **caspase inhibitors**)
IT Inflammation
(disease; **caspase inhibitors**)
IT Intestine, disease
(duodenum, ulcer, H. pylori-associated; **caspase inhibitors**)
IT Heart, disease
(failure; **caspase inhibitors**)
IT Kidney, disease
(glomerulonephritis; **caspase inhibitors**)
IT Transplant and Transplantation
(graft-vs.-host reaction; **caspase inhibitors**)
IT Shock (circulatory collapse)
(hemorrhagic; **caspase inhibitors**)
IT Heart, disease
(infarction; **caspase inhibitors**)
IT Intestine, disease
(inflammatory; **caspase inhibitors**)
IT Spinal cord, disease
(injury; **caspase inhibitors**)
IT Brain, disease
Heart, disease
(ischemia; **caspase inhibitors**)
IT Melanoma
(metastatic; **caspase inhibitors**)
IT Agranulocytosis
(neutropenia, autoimmune; **caspase inhibitors**)
IT Transplant rejection
(organ; **caspase inhibitors**)
IT Pancreas, disease
(pancreatitis; **caspase inhibitors**)
IT Peritoneum, disease
(peritonitis, inflammatory; **caspase inhibitors**)
IT Kidney, disease
(polyaptic; **caspase inhibitors**)
IT Skin, disease
(scar, scarring; **caspase inhibitors**)
IT Connective tissue, disease
(scleroderma; **caspase inhibitors**)
IT Shock (circulatory collapse)
(septic; **caspase inhibitors**)
IT Shigella
(shigellosis; **caspase inhibitors**)
IT Brain, disease
(stroke; **caspase inhibitors**)
IT Lupus erythematosus
(systemic; **caspase inhibitors**)
IT Brain, disease
(trauma; **caspase inhibitors**)
IT Stomach, disease
(ulcer, H. pylori-associated; **caspase inhibitors**)

IT Intestine, disease
(ulcerative colitis; **caspase inhibitors**)
IT Eye, disease
(uveitis; **caspase inhibitors**)
IT Hepatitis
(viral, chronic active; **caspase inhibitors**)
IT Infection
(viral; **caspase inhibitors**)
IT Fever and Hyperthermia
(yellow; **caspase inhibitors**)
IT 122191-40-6, **Caspase** 1 169592-56-7, **Caspase** 3
179241-78-2, **Caspase** 8 189258-14-8, **Caspase** 7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**caspase inhibitors**)
IT 476635-25-3P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(**caspase inhibitors**)
IT 476635-26-4 476635-27-5 476635-28-6 476635-29-7 476635-30-0
476635-31-1 476635-32-2 476635-33-3 476635-34-4 476635-35-5
476635-36-6 476635-37-7 476635-38-8 476635-39-9 476635-40-2
476635-41-3 476635-42-4 476635-43-5 476635-44-6 476635-45-7
476635-46-8 476635-47-9 476635-48-0 476635-49-1 476635-50-4
476635-51-5 476635-52-6 476635-53-7 476635-54-8 476635-55-9
476635-56-0 476635-57-1 476635-58-2 476635-59-3 476635-60-6
476635-61-7 476635-62-8 476635-63-9 476635-64-0 476635-65-1
476635-66-2 476635-67-3 476635-68-4 476635-69-5 476635-70-8
476635-71-9 476635-72-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**caspase inhibitors**)
IT 79-37-8, Oxalyl chloride 86-74-8, Carbazole 638-29-9, Valeryl chloride
5292-43-3, tert-Butyl bromoacetate 90719-32-7 161401-79-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(**caspase inhibitors**)
IT 112106-15-7P 143868-89-7P 225377-55-9P 476635-73-1P 476635-74-2P
476635-75-3P 476635-76-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**caspase inhibitors**)

L8 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2002:832795 CAPLUS
DOCUMENT NUMBER: 137:337787
TITLE: Heterocyclyldicarbamides as **caspase inhibitors**
INVENTOR(S): Diu-Hercend, Anita; Golec, Julian; Hercend, Thierry; **Knegtel, Ronald**; Lang, Paul; Miller, Andrew; Miller, Karen; **Mortimore, Michael**; Weber, Peter
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 94 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002085899	A1	20021031	WO 2002-US12638	20020419

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2443600	AA	20021031	CA 2002-2443600	20020419
US 2003096737	A1	20030522	US 2002-127324	20020419
EP 1381602	A1	20040121	EP 2002-723934	20020419

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

JP 2004527548	T2	20040909	JP 2002-583426	20020419

PRIORITY APPLN. INFO.:
US 2001-285051P P 20010419
WO 2002-US12638 W 20020419

OTHER SOURCE(S): MARPAT 137:337787

ED Entered STN: 01 Nov 2002

AB Title compds. I [Z = (un)substituted carbocyclic, aryl, saturated or partially saturated heterocycle, or heteroaryl; A = CO or SO2; Y = X3-X2-X1 wherein X3 = CH2 or X2 and X3 optionally form part of a Ph ring that is fused to the adjoining ring Q with provisions, X2 = O, S, NH or CH2 with NH and CH2 being optionally substituted or X2 and X1 may optionally form part of a Ph ring that is fused to adjoining ring Q, X1 = O, S, NH or CH2 which is optionally substituted; R1 = H, CN, CHN2, (un)substituted alkyl, aryl, etc.; R2 = CO2H, CH2CO2H, or optionally substituted esters, amides or isosteres thereof] are prepared and disclosed as caspase and TNF-alpha inhibitors. Thus, II was prepared in seven steps from (S)-piperidine carboxylate. This invention also relates to pharmaceutical compns. comprising these compds. The compds. and pharmaceutical compns. of this invention are particularly well suited for inhibiting caspase and TNF-alpha activity and consequently, can be advantageously used as agents against caspase-, interleukin-1- ("IL-1"), apoptosis-, interferon-γ inducing factor- (IGIF), interferon-γ- ("IFN-γ"), or TNF-alpha mediated diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. II demonstrated an IC50 value of less than 0.5 μM in inhibition of IL-1β secretion from peripheral blood mononuclear cells and an IC50 of less than 6 μM in the LPS induced TNF-alpha assay in whole blood. This invention also relates to methods for inhibiting caspase and TNF-alpha activity and decreasing IGIF production and IFN-γ production and methods for treating caspase-, interleukin-1, apoptosis-, and interferon-γ-, and TNF-alpha mediated diseases using the compds. and compns. of this invention.

IC ICM C07D417-06
ICS C07D401-06; C07D211-60; C07D405-06; C07D409-06; A61K031-445; A61P029-00

CC 27-16 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST carbamide heterocyclyldi prepn **caspase** TNF **inhibitor**; piperidinylcarbamide prepn **caspase** TNF **inhibitor**

IT Hepatitis
(B, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Hepatitis
(C, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Intestine, disease

(Crohn's, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Encephalitis
(HIV related; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Nervous system, disease
(Huntington's chorea, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Sarcoma
(Kaposi's, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Spinal muscular atrophy
(X-linked spinal and bulbar muscular atrophy, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Heart, disease
(acute and chronic; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Leukemia
(acute myelogenous, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Respiratory distress syndrome
(adult, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Liver, disease
(alc., treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Nervous system, disease
(amyotrophic lateral sclerosis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Antiarteriosclerotics
(antiatherosclerotics, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Aneurysm
(aortic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Dermatitis
(atopic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Stomach, disease
(autoimmune gastritis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Anemia (disease)
(autoimmune hemolytic anemia, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Thyroid gland, disease
(autoimmune thyroiditis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors**

from optically active piperidine carboxylates)
IT Nervous system, disease
(central, demyelination, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Nervous system, disease
(central, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Leukemia
(chronic myelocytic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Dermatitis
(contact, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Artery
(coronary, bypass graft; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Disease, animal
(degenerative, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Infection
(dengue, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Eye, disease
(diabetic retinopathy, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Platelet (blood)
(disease, thrombocytopenia; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Intestine, disease
(duodenum, ulcer, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Heart, disease
(failure, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Drugs
(gastrointestinal; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Kidney, disease
(glomerulonephritis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Transplant and Transplantation
(graft-vs.-host reaction; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Shock (circulatory collapse)
(hemorrhagic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Skin, disease

(hypertrophic scar, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Heart, disease
(infarction, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Eye, disease
(inflammation, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Intestine, disease
(inflammatory, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Interleukin 1 receptors
Tumor necrosis factor receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Spinal cord, disease
(injury, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Brain, disease
Heart, disease
(ischemia, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Eye, disease
(keratoconjunctivitis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Eye, disease
(macula, degeneration, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Melanoma
(metastatic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Agranulocytosis
(neutropenia, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Anti-inflammatory agents
(nonsteroidal; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Pancreas, disease
(pancreatitis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Peritoneum, disease
(peritonitis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Kidney, disease
(polycystic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Transplant rejection
(prevention of corneal graft rejection; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Apoptosis
(prevention of organ apoptosis after burn injury; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Transplant rejection
(prevention of organ; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Eye, disease
(retinopathy, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Connective tissue, disease
(scleroderma, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Arthritis
Shock (circulatory collapse)
(septic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Aging, animal
Anti-AIDS agents
Anti-Alzheimer's agents
Anti-infective agents
Antiarthritics
Antiasthmatics
Anticonvulsants
Antidiabetic agents
Antiparkinsonian agents
Antirheumatic agents
Antitumor agents
Antiviral agents
Asymmetric synthesis and induction
Cardiovascular agents
Drug delivery systems
Drug interactions
Human
Multiple myeloma
Nervous system agents
Tuberculostatics
(stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Brain, disease
(stroke, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Inflammation
(systemic inflammatory response syndrome, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Lupus erythematosus
(systemic, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
IT Multiple sclerosis
Osteoporosis
(therapeutic agents; stereoselective preparation of piperidinylcarbamides as

caspase inhibitors from optically active piperidine carboxylates)

IT Brain, disease
Injury
(trauma, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Interleukin 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of IL-1 mediated diseases; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Shigella
(treatment of Shigellosis; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Multiple myeloma
(treatment of bone disorders; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Cell death
(treatment of disease associated with; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Joint, anatomical
(treatment of injury of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Tumor necrosis factors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(treatment of prevention of TNF-α mediated disease; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Apoptosis
(treatment of prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT AIDS (disease)
Alopecia
Alzheimer's disease
Anorexia
Asthma
Atherosclerosis
Autoimmune disease
Bone, disease
Burn
Cachexia
Diabetes mellitus
Epilepsy
Graves' disease
Hepatitis GB virus C/G
Infection
Inflammation
Japanese encephalitis virus
Kidney, disease
Leukemia
Meningitis
Multiple organ failure
Multiple sclerosis
Myasthenia gravis
Myelodysplastic syndromes
Neoplasm

Osteoarthritis
Osteoporosis
Parkinson's disease
Periodontium, disease
Prion diseases
Psoriasis
Rheumatoid arthritis
Sepsis
Sjogren's syndrome
Skin, disease
Spinal muscular atrophy
Tuberculosis
(treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Stomach, disease
(ulcer, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Intestine, disease
(ulcerative colitis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Eye, disease
(uveitis, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Hepatitis
(viral, chronic active, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Infection
(viral, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT Fever and Hyperthermia
(yellow, treatment or prevention of; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT 474010-52-1P 474010-55-4P 474010-56-5P 474010-63-4P 474010-68-9P
474010-71-4P 474010-76-9P 474010-78-1P 474010-80-5P 474010-82-7P
474010-84-9P 474010-86-1P 474010-89-4P 474010-90-7P 474010-99-6P
474011-04-6P 474011-10-4P 474011-16-0P 474011-20-6P 474011-22-8P
474011-24-0P 474011-28-4P 474011-31-9P 474011-34-2P 474011-37-5P
474011-41-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT 98-80-6, Phenyl boronic acid 98-88-4, Benzoyl chloride 486-73-7, 1-Isoquinoline carboxylic acid 716-76-7, 3-Biphenylcarboxylic acid 3105-95-1 5834-16-2 7113-10-2, 2-Phenylthiazole-4-carboxylic acid 13139-17-8, N-(Benzyloxycarbonyloxy)succinimide 18650-39-0 161401-79-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)

IT 23806-25-9P 28697-11-2P 38239-46-2P 60343-61-5P 160417-30-1P
273921-32-7P 376347-03-4P 474011-55-7P 474011-58-0P 474011-61-5P
474011-64-8P 474011-67-1P 474011-71-7P 474011-72-8P 474011-77-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT

(Reactant or reagent)
(stereoselective preparation of piperidinylcarbamides as **caspase inhibitors** from optically active piperidine carboxylates)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2002:220587 CAPLUS
DOCUMENT NUMBER: 136:247611
TITLE: Preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases
INVENTOR(S): Charrier, Jean-Damien; **Knegtel, Ronald**; **Mortimore, Michael**
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2002022611	A2	20020321	WO 2001-US28450		20010912
WO 2002022611	A3	20021031			
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
CA 2418720	AA	20020321	CA 2001-2418720		20010912
AU 2001090795	A5	20020326	AU 2001-90795		20010912
US 2002058630	A1	20020516	US 2001-951006		20010912
US 6800619	B2	20041005			
EP 1317454	A2	20030611	EP 2001-970836		20010912
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2004509120	T2	20040325	JP 2002-526864		20010912
PRIORITY APPLN. INFO.:			US 2000-232573P	P	20000913
			WO 2001-US28450	W	20010912

OTHER SOURCE(S): MARPAT 136:247611
ED Entered STN: 22 Mar 2002
AB Title compds. [R4R3NCOACONHCH(COR1)CH2R2; A = piperidine, tetrahydroquinoline, tetrahydroisoquinoline; R1 = H, CN, CHN2, R, CH2Y; R = aliphatic, aryl, aralkyl; Y = electroneg. leaving group; R2 = COOH, CH2COOH, esters, amides, isosteres; R3 = H, aralkyl, C1-6alkph.; R4 = aryl, heterocycle; R3R4 with N form monocyclic, bicyclic, tricyclic ring] are prepared as caspase inhibitors for treating IL-1 mediated diseases, apoptosis mediated diseases, inflammatory diseases, etc. Thus, title compound I was prepared and was tested for inhibition of IL-1β secretion from human PBMC and anti-Fas induced apoptosis assay.
IC ICM C07D417-06
ICS C07D401-06; C07D413-06; C07D471-04; C07D495-04; C07D513-04; A61K031-5415; A61K031-473; A61P029-00
CC 28-18 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63
ST benzthiazinecarbonylpiperidinecarbamide prepn **caspase**

inhibitor; quinolinecarbonylpiperidinecarbamide prepn
caspase inhibitor; carbazolecarbonylpiperidinecarbamide
prepn **caspase inhibitor**; phenanthridinecarbonylpiperid
inecarbamide prepn **caspase inhibitor**

IT Intestine, disease
(Crohn's; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Respiratory distress syndrome
(adult; preparation of heterocyclyldicarbamides as **caspase inhibitors**)

IT Dermatitis
(atopic; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Stomach, disease
(autoimmune gastritis; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Anemia (disease)
(autoimmune hemolytic anemia; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Thyroid gland, disease
(autoimmune thyroiditis; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Disease, animal
(degenerative; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Platelet (blood)
(disease, thrombocytopenia; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Kidney, disease
(glomerulonephritis; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Transplant and Transplantation
(host-vs.-graft reaction; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Intestine, disease
(inflammatory; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Agranulocytosis
(neutropenia; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Pancreas, disease
(pancreatitis; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Peritoneum, disease
(peritonitis; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Anti-inflammatory agents
Antiasthmatics
Antidiabetic agents
Apoptosis
Bone, disease
Cell death
Human
Myasthenia gravis
Myelodysplastic syndromes
Osteoarthritis

Osteoporosis
Psoriasis
Rheumatoid arthritis
Transplant rejection
Wound
(preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Interleukin 1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Disease, animal
(proliferative; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Connective tissue, disease
(scleroderma; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Lupus erythematosus
(systemic; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Eye, disease
(uveitis; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT Hepatitis
(viral, chronic active; preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT 186322-81-6, Caspase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT 404838-91-1P 404838-92-2P 404838-93-3P 404838-94-4P 404838-95-5P
404838-96-6P 404838-97-7P 404838-98-8P 404838-99-9P 404839-00-5P
404839-01-6P 404839-02-7P 404839-03-8P 404839-04-9P 404839-05-0P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT 109-01-3, N-Methylpiperazine 109-89-7, Diethylamine, reactions
758-96-3 18650-39-0 18956-87-1, 10H-Phenothiazine-10-carbonyl chloride
161401-79-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

IT 404839-06-1P 404839-07-2P 404839-08-3P 404839-09-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of heterocyclyldicarbamides as **caspase inhibitors** and uses for treating IL-1 mediated diseases)

L8 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 8
ACCESSION NUMBER: 2001:730702 CAPLUS
DOCUMENT NUMBER: 135:273216
TITLE: Preparation of carbamate **caspase inhibitors**
INVENTOR(S): Bebbington, David; Charrier, Jean-Damien; Kay, David; **Knegtel, Ronald**; Golec, Julian; **Mortimore, Michael**; **Studley, John**
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001072707	A2	20011004	WO 2001-US10182	20010329
WO 2001072707	A3	20020523		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2403959	AA	20011004	CA 2001-2403959	20010329
US 2002028803	A1	20020307	US 2001-821161	20010329
US 6689784	B2	20040210		
EP 1268425	A2	20030102	EP 2001-922868	20010329
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001009588	A	20030204	BR 2001-9588	20010329
JP 2003528855	T2	20030930	JP 2001-570620	20010329
EE 200200550	A	20040216	EE 2002-550	20010329
NZ 521639	A	20040528	NZ 2001-521639	20010329
ZA 2002007483	A	20030918	ZA 2002-7483	20020918
BG 107136	A	20030530	BG 2002-107136	20020923
NO 2002004661	A	20021126	NO 2002-4661	20020927
US 2004053920	A1	20040318	US 2003-645043	20030821
PRIORITY APPLN. INFO.:			US 2000-192826P P	20000329
			US 2001-821161 A3	20010329
			WO 2001-US10182 W	20010329

OTHER SOURCE(S): MARPAT 135:273216
ED Entered STN: 07 Oct 2001
AB Carbamate derivs. I [Z is O, S; R1 is H, CHN2, R (R is C1-12 aliphatic, aryl, aralkyl, heterocyclyl, orheterocyclylalkyl), CH2OR, CH2SR, or CH2Y (Y is an electroneg. leaving group); R2 is CO2H, CH2CO2H or esters, amides or isosteres; R3 is a group capable of fitting into the S2 subsite of a caspase enzyme; R4R5N is a mono-, bi- or tricyclic heterocyclic ring system] were prepared as caspase inhibitors. The compds. are effective inhibitors of apoptosis and IL-1β secretion. Thus, compound II was prepared by amidation of (S)-3-methyl-2-(carbazole)carbamoyloxybutyric acid (preparation given) with 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester, followed by oxidation of the hydroxy group using Dess-Martin periodinane and ester cleavage.
IC ICM C07D209-00
CC 34-2 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST amino acid carbamate prepn **caspase inhibitor**
IT Hepatitis
(B; preparation of carbamate **caspase inhibitors**)
IT Hepatitis
(C; preparation of carbamate **caspase inhibitors**)
IT Intestine, disease
(Crohn's; preparation of carbamate **caspase inhibitors**)
IT Nervous system
(Huntington's chorea; preparation of carbamate **caspase inhibitors**)
IT Sarcoma

(Kaposi's; preparation of carbamate **caspase inhibitors**)
IT Spinal muscular atrophy
(X-linked spinal and bulbar muscular atrophy; preparation of carbamate **caspase inhibitors**)
IT Leukemia
(acute myelogenous; preparation of carbamate **caspase inhibitors**)
IT Respiratory distress syndrome
(adult; preparation of carbamate **caspase inhibitors**)
IT Nervous system
(amyotrophic lateral sclerosis; preparation of carbamate **caspase inhibitors**)
IT Dermatitis
(atopic; preparation of carbamate **caspase inhibitors**)
IT Stomach, disease
(autoimmune gastritis; preparation of carbamate **caspase inhibitors**)
IT Anemia (disease)
(autoimmune hemolytic anemia; preparation of carbamate **caspase inhibitors**)
IT Thyroid gland, disease
(autoimmune thyroiditis; preparation of carbamate **caspase inhibitors**)
IT Leukemia
(chronic myelocytic; preparation of carbamate **caspase inhibitors**)
IT Disease, animal
(degenerative; preparation of carbamate **caspase inhibitors**)
IT Infection
(dengue; preparation of carbamate **caspase inhibitors**)
IT Heart, disease
(failure; preparation of carbamate **caspase inhibitors**)
IT Ulcer
(gastric and duodenal; preparation of carbamate **caspase inhibitors**)
IT Kidney, disease
(glomerulonephritis; preparation of carbamate **caspase inhibitors**)
IT Transplant and Transplantation
(graft-vs.-host reaction; preparation of carbamate **caspase inhibitors**)
IT Shock (circulatory collapse)
(hemorrhagic; preparation of carbamate **caspase inhibitors**)
IT Antitumor agents
(immunotherapy; preparation of carbamate **caspase inhibitors**)
IT Heart, disease
(infarction; preparation of carbamate **caspase inhibitors**)
IT Intestine, disease
(inflammatory; preparation of carbamate **caspase inhibitors**)
IT Spinal cord
(injury; preparation of carbamate **caspase inhibitors**)
IT Brain, disease
Heart, disease
(ischemia; preparation of carbamate **caspase inhibitors**)
IT Antitumor agents
(leukemia; preparation of carbamate **caspase inhibitors**)
IT Melanoma

(metastatic; preparation of carbamate **caspase inhibitors**
)
IT Agranulocytosis
(neutropenia, autoimmune; preparation of carbamate **caspase inhibitors**)
IT Pancreas, disease
(pancreatitis; preparation of carbamate **caspase inhibitors**
)
IT Peritoneum
(peritonitis, inflammatory; preparation of carbamate **caspase inhibitors**)
IT Aging, animal
Alcoholism
Alopecia
Alzheimer's disease
Anti-inflammatory agents
Antiasthmatics
Antidiabetic agents
Antirheumatic agents
Antiviral agents
Apoptosis
Atherosclerosis
Autoimmune disease
Bone, disease
Burn
Cell death
Encephalitis
Epilepsy
Graves' disease
Heart, disease
Human immunodeficiency virus
Immunotherapy
Infection
Kidney, disease
Liver, disease
Lupus erythematosus
Meningitis
Multiple myeloma
Multiple sclerosis
Myasthenia gravis
Myelodysplastic syndromes
Osteoarthritis
Osteoporosis
Parkinson's disease
Prion diseases
Psoriasis
Sepsis
Spinal muscular atrophy
Transplant and Transplantation
Tuberculosis
(preparation of carbamate **caspase inhibitors**)
IT Amino acids, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of carbamate **caspase inhibitors**)
IT Connective tissue
(scleroderma; preparation of carbamate **caspase inhibitors**
)
IT Shock (circulatory collapse)
(septic; preparation of carbamate **caspase inhibitors**)
IT Brain, disease

(stroke; preparation of carbamate **caspase inhibitors**)
IT Platelet (blood)
(thrombocytopenia; preparation of carbamate **caspase inhibitors**)
IT Brain, disease
(trauma; preparation of carbamate **caspase inhibitors**)
IT Intestine, disease
(ulcerative colitis; preparation of carbamate **caspase inhibitors**)
IT Eye, disease
(uveitis; preparation of carbamate **caspase inhibitors**)
IT Hepatitis
(viral, chronic active; preparation of carbamate **caspase inhibitors**)
IT Fever and Hyperthermia
(yellow; preparation of carbamate **caspase inhibitors**)
IT 363154-80-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of carbamate **caspase inhibitors**)
IT 363154-82-9P 363154-84-1P 363154-86-3P 363154-88-5P 363154-90-9P
363154-92-1P 363154-94-3P 363154-96-5P 363154-98-7P 363155-00-4P
363155-02-6P 363155-04-8P 363155-06-0P 363155-08-2P 363155-10-6P
363155-12-8P 363155-14-0P 363155-16-2P 363155-18-4P 363155-20-8P
363155-22-0P 363155-24-2P 363155-26-4P 363155-28-6P 363155-30-0P
363155-32-2P 363155-34-4P 363155-36-6P 363155-38-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of carbamate **caspase inhibitors**)
IT 122191-40-6, caspase-1 169592-56-7, caspase-3 179241-78-2, caspase-8
189258-14-8, caspase-7
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of carbamate **caspase inhibitors**)
IT 86-74-8, Carbazole 92-39-7, 2-Chlorophenothiazine 109-89-7, Diethylamine, reactions 496-15-1, Indoline 503-38-8, Diphosgene 530-62-1 577-19-5, 2-Bromonitrobenzene 1679-18-1, 4-Chlorophenylboronic acid 3519-30-0 18956-87-1, Phenothiazine-10-carbonyl chloride 87413-09-0, Dess-Martin periodinane 161401-79-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of carbamate **caspase inhibitors**)
IT 6271-80-3P 10537-08-3P 36798-98-8P 363155-39-9P 363155-41-3P
363155-43-5P 363155-45-7P 363155-47-9P 363155-51-5P 363155-52-6P
363155-54-8P 363155-56-0P 363155-58-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carbamate **caspase inhibitors**)

L8 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:1036696 CAPLUS
TITLE: **Caspase inhibitors** and uses thereof
INVENTOR(S): Brenchley, Guy; Charrier, Jean-Damien; Durrant, Steven; **Knegtel, Ronald**; **Mortimore, Michael**; **Studley, John R.**
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 36 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004242494	A1	20041202	US 2004-855699	20040527
WO 2004106304	A2	20041209	WO 2004-US16706	20040527

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2003-473622P P 20030527
ED Entered STN: 03 Dec 2004
AB The present invention provides a compound of formula I: 1 wherein R 1 , R 2 , R 3 , R 4 , and R 5 are as defined herein. The present invention also provides pharmaceutical compositions and methods using such compositions for treating a caspase-mediated diseases and processes for preparing the compounds of the invention.
IC ICM A61K038-04
ICS A61K031-4415; C07D041-02
NCL 514019000; 514346000; 546268100; 546291000
CC 28 (Heterocyclic Compounds (More Than One Hetero Atom))

L8 ANSWER 10 OF 11 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2004:442479 BIOSIS
DOCUMENT NUMBER: PREV200400448664
TITLE: **Caspase inhibitors** and uses thereof.
AUTHOR(S): Charrier, Jean-Damien [Inventor, Reprint Author]; **Knegtel, Ronald** [Inventor]; **Mortimore, Michael** [Inventor]
CORPORATE SOURCE: Wantage, UK
ASSIGNEE: Vertex Pharmaceuticals Incorporated
PATENT INFORMATION: US 6800619 October 05, 2004
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Oct 5 2004) Vol. 1287, No. 1. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Nov 2004
Last Updated on STN: 17 Nov 2004
ABSTRACT:Described herein are compounds that are useful as **caspase** ***inhibitors*** having the formula: ##STR1## wherein Ring A is an optionally substituted piperidine, tetrahydroquinoline or tetrahydroisoquinoline ring; R1 is hydrogen, CN, CHN2, R, or CH2 Y; R is an optionally substituted group selected from an aliphatic group, an aryl group, or an aralkyl group; Y is an electronegative leaving group; R2 is CO2 H, CH2 CO2 H, or esters, amides or isosteres thereof; and R3 is hydrogen, an optionally substituted aryl group, an optionally substituted aralkyl group, or an optionally substituted C1-6 aliphatic group, R4 is an optionally substituted group selected from an aryl

group or a heterocyclyl group, or R3 and R4 taken together with the nitrogen to which they are attached optionally form a substituted or unsubstituted monocyclic, bicyclic or tricyclic ring.
NAT. PATENT. CLASSIF.:514183000
CONCEPT CODE: Enzymes - General and comparative studies: coenzymes 10802
Physiology - General 12002
Pathology - General 12502
Pathology - Therapy 12512
Cardiovascular system - Blood vessel pathology 14508
Nervous system - Pathology 20506
Pharmacology - General 22002
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Immunology - Immunopathology, tissue immunology 34508
INDEX TERMS: Major Concepts
Enzymology (Biochemistry and Molecular Biophysics); Human Medicine (Medical Sciences); Pharmacology; Physiology
INDEX TERMS: Diseases
autoimmune disease: immune system disease
Autoimmune Diseases (MeSH)
INDEX TERMS: Diseases
cancer: neoplastic disease
Neoplasms (MeSH)
INDEX TERMS: Diseases
ischemia: vascular disease
Ischemia (MeSH)
INDEX TERMS: Diseases
neurodegenerative disease: nervous system disease
Neurodegenerative Diseases (MeSH)
INDEX TERMS: Chemicals & Biochemicals
caspase inhibitors: enzyme **inhibitor**-drug
ORGANISM: Classifier
Hominidae 86215
Super Taxa
Primates; Mammalia; Vertebrata; Chordata; Animalia
Organism Name
human (common)
Taxa Notes
Animals, Chordates, Humans, Mammals, Primates, Vertebrates

L8 ANSWER 11 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-022574 [02] WPIDS
DOC. NO. CPI: C2004-007024
TITLE: Identification of a compound that decreases tumor necrosis factor-alpha levels in a cell culture, useful to treat e.g. septic arthritis and periodontal diseases, comprises administration of compound to the cell culture.
DERWENT CLASS: B05
INVENTOR(S): DIU-HERCEND, A; GOLEC, J; HERCEND, T; LANG, P; MILLER, K; **MORTIMORE, M**; WEBER, P
PATENT ASSIGNEE(S): (DIUH-I) DIU-HERCEND A; (GOLE-I) GOLEC J; (HERC-I) HERCEND T; (LANG-I) LANG P; (MILL-I) MILLER K; (MORT-I) MORTIMORE M; (WEBE-I) WEBER P; (VERT-N) VERTEX PHARM INC
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG	MAIN IPC

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     WO 2003088917   A2 20031030 (200402)* EN  182 A61K000-00
        RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS
            LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR
            KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL
            PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU
            ZA ZM ZW
     US 2004048797   A1 20040311 (200419)          A61K038-06
     AU 2003225088   A1 20031103 (200438)          A61K000-00

APPLICATION DETAILS:

     PATENT NO      KIND                  APPLICATION         DATE
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     WO 2003088917   A2                  WO 2003-US12262     20030417
     US 2004048797   A1 Provisional      US 2002-374434P     20020419
                                         US 2003-419327      20030417
     AU 2003225088   A1                  AU 2003-225088      20030417

FILING DETAILS:

     PATENT NO       KIND                   PATENT NO
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     AU 2003225088   A1 Based on          WO 2003088917

PRIORITY APPLN. INFO: US 2002-374434P      20020419; US
                      2003-419327       20030417
INT. PATENT CLASSIF.:
           MAIN:      A61K000-00; A61K038-06
      SECONDARY:      A61K038-04; A61K038-05; C07K005-04; C07K005-06
BASIC ABSTRACT:
     WO2003088917 A UPAB: 20040107
     NOVELTY - Identifying a compound that decreases tumor necrosis
     factor-alpha levels in a cell culture comprises administration of compound
     (I) to the cell culture and composition of the tumor necrosis factor-alpha
     present with an untreated culture.
          DETAILED DESCRIPTION - Identifying a compound that decreases tumor
     necrosis factor-alpha levels in a cell culture comprises administration of
     the compound (I) to the cell culture and composition of the tumor necrosis
     factor- alpha (TNF- alpha ) present with an untreated culture. (I) Is a
     compound as described in WO00/55114, WO00/55127, WO00/61542, WO01/05772,
     WO01/10383, WO01/16093, WO01/42216, WO01/72707, WO01/90070, WO01/94351,
     WO02/094263, WO02/42278, US6,184,210, US6,184,244, US6,187,771,
     US6,197,750, US6,242,422, WO02/22611, US2002/0058630 or US10/127324.
          AN INDEPENDENT CLAIM is also included for a kit comprises a
     caspase inhibitor and a tool for measuring TNF- alpha
     level or activity.
          ACTIVITY - Antiinflammatory; Vasotropic; CNS-Gen; Neuroprotective;
     Antiarthritic; Ophthalmological; Antidiabetic; Immunosuppressive;
     Immunomodulator; Anabolic; Eating-disorders-Gen; Antirheumatic;
     Osteopathic; Antibacterial; Respiratory-Gen; Cerebroprotective;
     Antimalarial; Antipyretic; Anti-HIV; Virucide; Vulnerary; Antiulcer;
     Gastrointestinal-Gen; Dermatological; Antiallergic; Antiasthmatic.
          MECHANISM OF ACTION - TNF- alpha Inhibitor.
          In a test using human blood, quinazolino-3-(3-methyl
     acetamido)-acetyl fluoro glutamic acid inhibited TNF- alpha with an IC50
     of less than 500 nM.
          USE - (I) Is used to treat inflammatory diseases such as inflammatory
     diseases of the central nervous system, demyelinating diseases of the
     nervous system, multiple sclerosis, septic arthritis, aneurismal aortic
```

disease, traumatic joint injury, periodontal disease, macular degeneration, diabetic retinopathy, ocular inflammation, keratoconus, Sjogren's syndrome, corneal graft rejection, cachexia, anorexia, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, general sepsis, gram-negative sepsis, septic shock, endotoxic shock, toxic shock syndrome, adult respiratory distress syndrome (ARDS), cerebral malaria, chronic pulmonary inflammatory disease, silicosis, asbestosis, pulmonary sarcoidosis, bone resorption diseases, graft versus host reactions, allograft rejections, fever and myalgias due to bacterial or viral infections, influenza, cachexia secondary to acquired immune deficiency syndrome (AIDS), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, pyresis, a number of autoimmune diseases, systemic lupus erythematosus, allergic traumatic and other injurious disorders including asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, eosiniophilic granuloma, ulcerative colitis, reperfusion injury of the myocardium and brain and chronic glomerulonephritis.

ADVANTAGE - (I) Have improved cell penetration and pharmacokinetic properties and as a consequence of their potency, have improved efficacy against disease where caspases and/or TNF- alpha are implicated.

Dwg.0/20

FILE SEGMENT: CPI
FIELD AVAILABILITY: AB; GI; DCN
MANUAL CODES: CPI: B06-A01; B06-B01; B06-D13; B06-D16; B06-D17; B06-E03; B06-E04; B06-F03; B06-F04; B06-F05; B07-B02; B07-D05; B07-D13; B07-E01; B14-A01; B14-A02; B14-A03B; B14-C03; B14-C04; B14-C06; B14-C09; B14-E08; B14-E10; B14-E11; B14-F02D; B14-G02A; B14-G02D; B14-J01; B14-K01; B14-K01A; B14-L06; B14-N01; B14-N03; B14-N16; B14-N17; B14-S04

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FILE 'REGISTRY' ENTERED AT 15:11:32 ON 10 DEC 2004
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STRUCTURE FILE UPDATES:     9 DEC 2004  HIGHEST RN 796026-09-0
DICTIONARY FILE UPDATES:    9 DEC 2004  HIGHEST RN 796026-09-0

TSCA INFORMATION NOW CURRENT THROUGH MAY 21, 2004

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

L13                 STR
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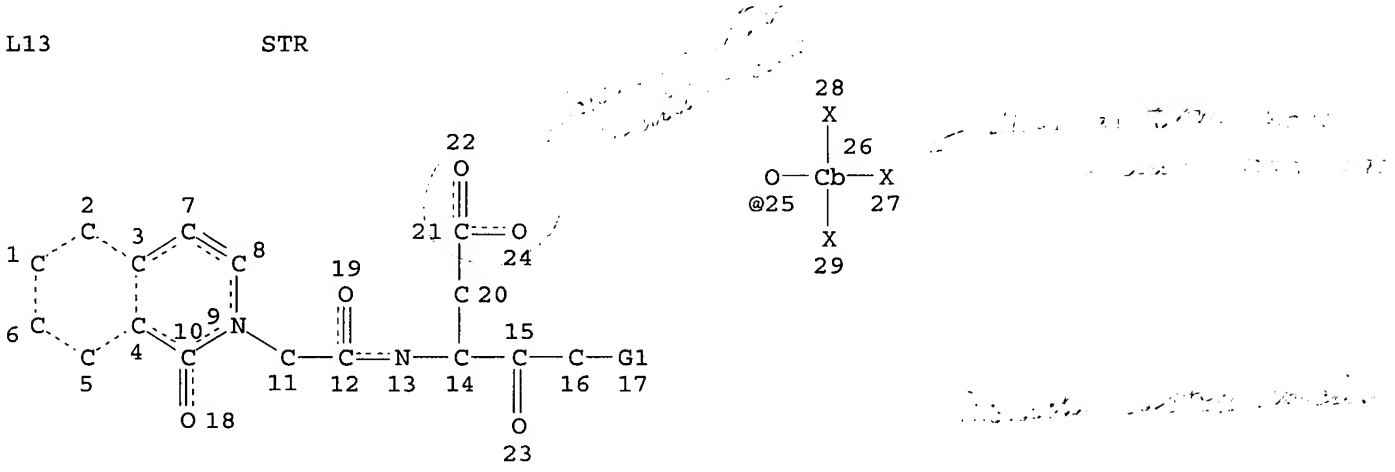


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DEFAULT ECLEVEL IS LIMITED

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RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  29

STEREO ATTRIBUTES: NONE
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FILE 'CAPLUS' ENTERED AT 15:11:32 ON 10 DEC 2004
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FILE 'USPATFULL' ENTERED AT 15:11:32 ON 10 DEC 2004
CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'TOXCENTER' ENTERED AT 15:11:32 ON 10 DEC 2004
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L18 15 L16

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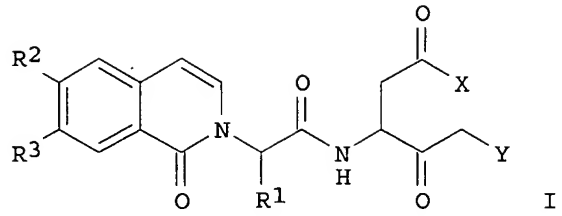
PROCESSING COMPLETED FOR L18
L19 10 DUP REM L18 (5 DUPLICATES REMOVED)
ANSWERS '1-6' FROM FILE CAPLUS
ANSWERS '7-10' FROM FILE USPATFULL

=> d ibib ed abs hitstr 1-10; fil hom

L19 ANSWER 1 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2004:565214 CAPLUS
DOCUMENT NUMBER: 141:106388
TITLE: Preparation of 4-oxo-3-(1-oxo-1H-isoquinolin-2-ylacetylamino)-pentanoic acid ester and amide derivatives as caspase inhibitors
INVENTOR(S): Charrier, Jean-Damien; Mortimore, Michael; Studley, John R.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004058718	A1	20040715	WO 2003-US40870		20031222
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW					
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004192612	A1	20040930	US 2003-743563		20031222
PRIORITY APPLN. INFO.:			US 2002-435133P	P	20021220

OTHER SOURCE(S): MARPAT 141:106388
ED Entered STN: 15 Jul 2004
GI



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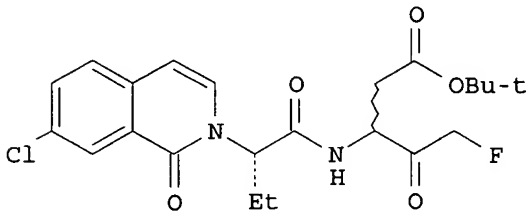


II

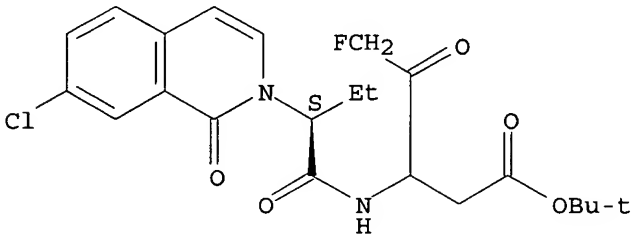
AB The title compds. of formula I [X = alkoxy, (substituted) NH2, etc.; Y = halo, trifluorophenoxy, tetrafluorophenoxy; R1 = alkyl; R2, R3 = H, halo, OCF3, CN, CF3] are prepared The present invention also provides pharmaceutical compns. and methods using such compns. for treating a caspase-mediated disease, particularly in the central nervous system. Thus, II was prepared from 7-chloroisochromen-1-one (preparation given), (S)-2-aminobutyric acid tert-Bu ester and 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester.

IT **640286-59-5P 721397-83-7P**
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

RN 640286-59-5 CAPLUS

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

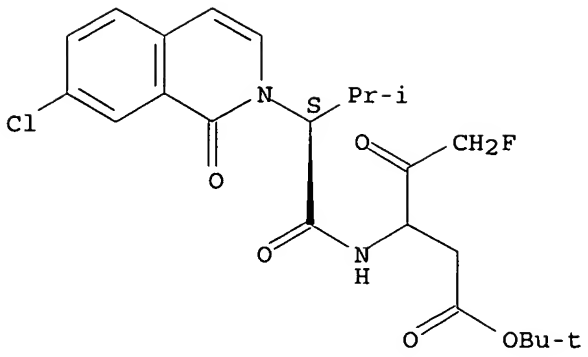
Absolute stereochemistry.



RN 721397-83-7 CAPLUS

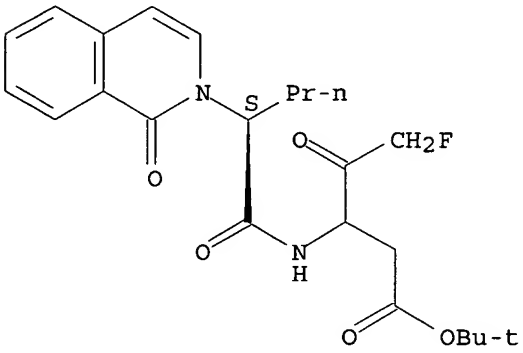
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



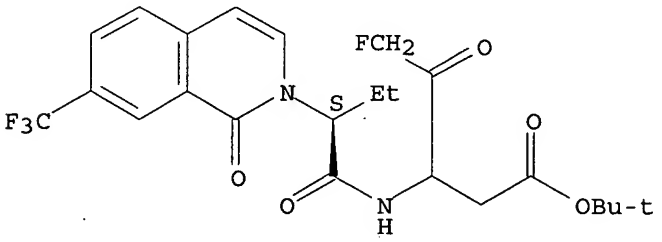
RN 721397-81-5 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)pentyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 721397-82-6 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

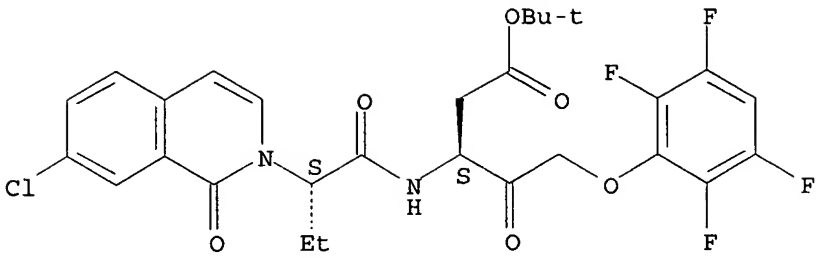
Absolute stereochemistry.



t-butyl ester of elected species

RN 721397-84-8 CAPLUS
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

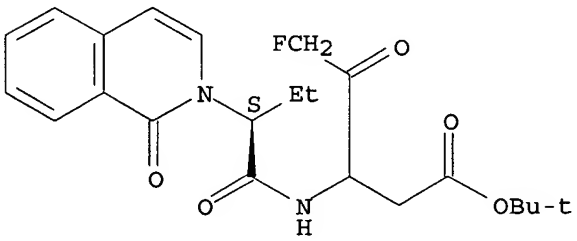


IT **721397-79-1P 721397-80-4P 721397-81-5P**
721397-82-6P 721397-84-8P 721397-85-9P
721397-86-0P 721397-87-1P 721397-88-2P
721397-89-3P 721397-90-6P 721397-91-7P
721397-92-8P 721397-93-9P 721397-94-0P
721397-95-1P 721397-96-2P 721397-97-3P
721397-98-4P 721397-99-5P 721398-00-1P
721398-01-2P 721398-02-3P 721398-03-4P
721398-04-5P 721398-05-6P 721398-06-7P
721398-07-8P 721398-08-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

RN 721397-79-1 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

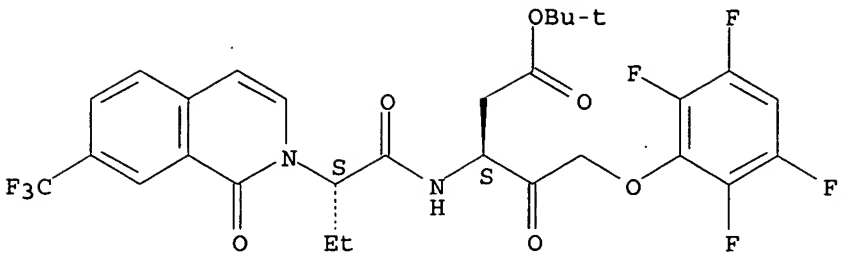
Absolute stereochemistry.



RN 721397-80-4 CAPLUS

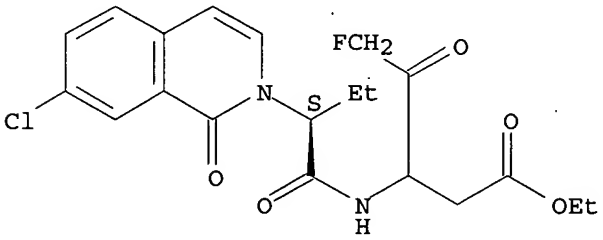
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-3-methyl-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



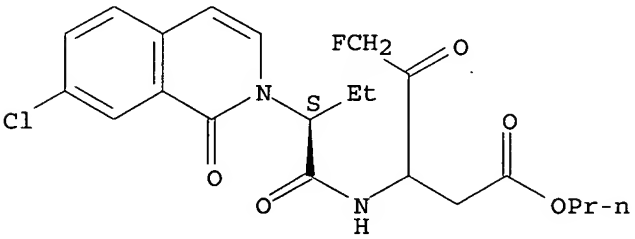
RN 721397-85-9 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



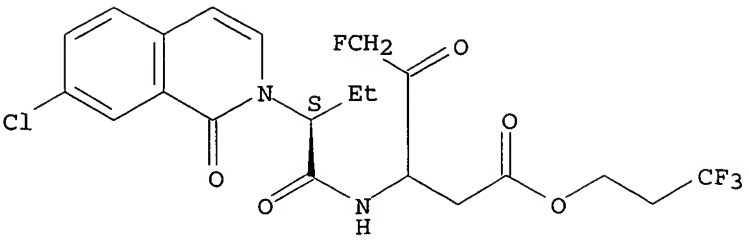
RN 721397-86-0 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



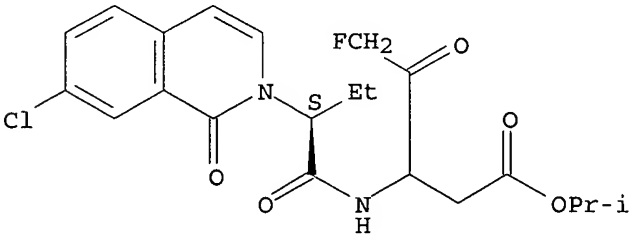
RN 721397-87-1 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 3,3,3-trifluoropropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



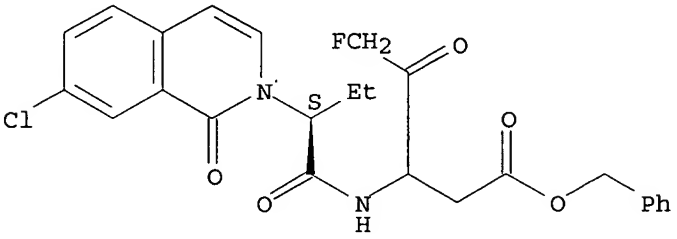
RN 721397-88-2 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1-methylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



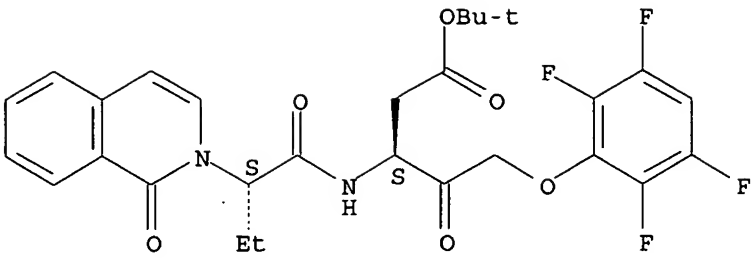
RN 721397-89-3 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



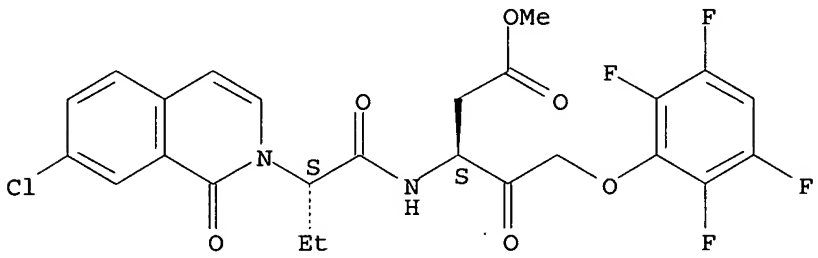
RN 721397-90-6 CAPLUS
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



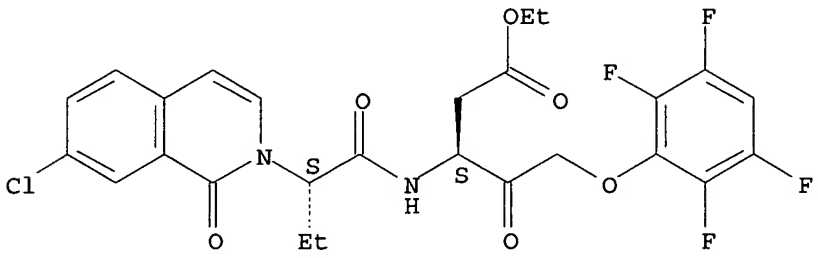
RN 721397-91-7 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, methyl ester, (3S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



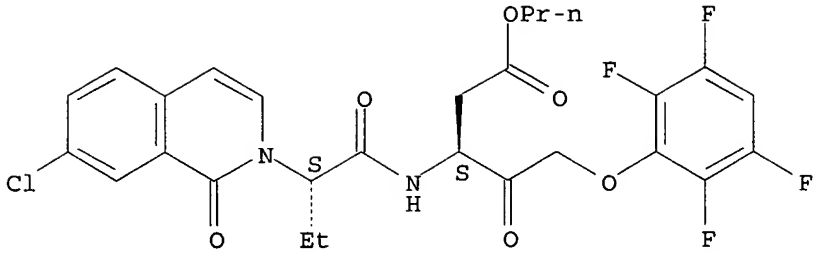
RN 721397-92-8 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, ethyl ester, (3S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



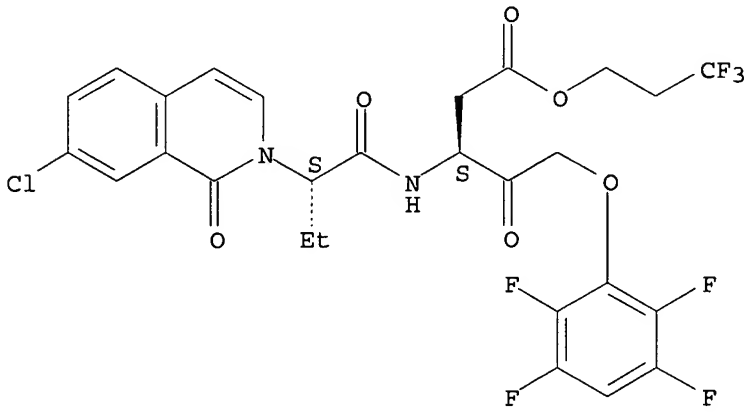
RN 721397-93-9 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, propyl ester, (3S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



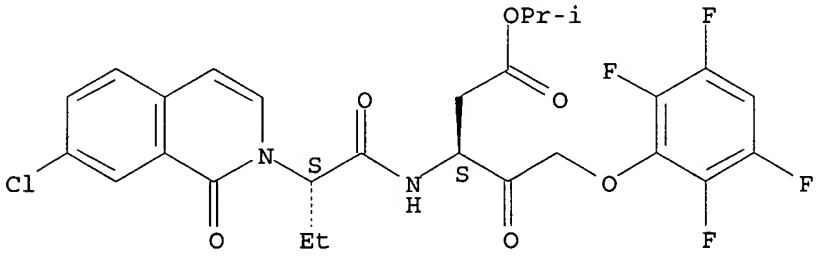
RN 721397-94-0 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 3,3,3-trifluoropropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



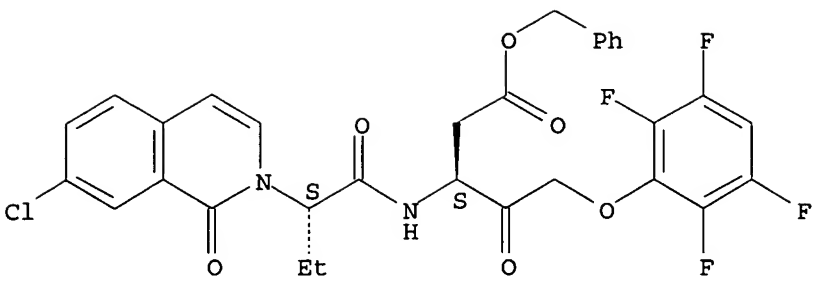
RN 721397-95-1 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-methylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



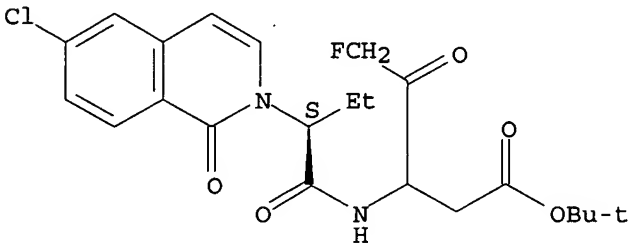
RN 721397-96-2 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, phenylmethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



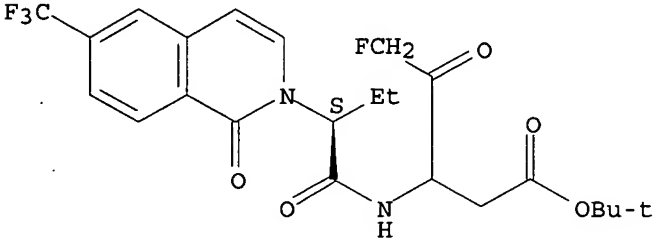
RN 721397-97-3 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(6-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 721397-98-4 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-6-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

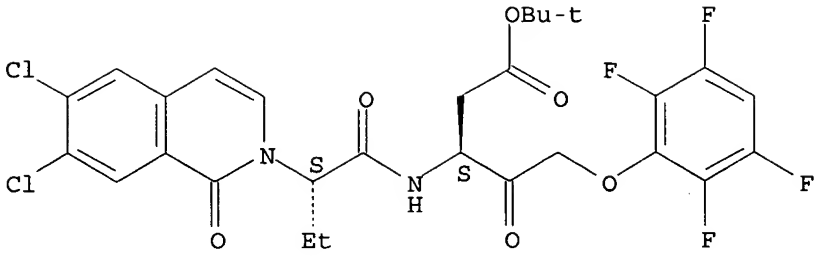
Absolute stereochemistry.



t-butyl ester of elected species

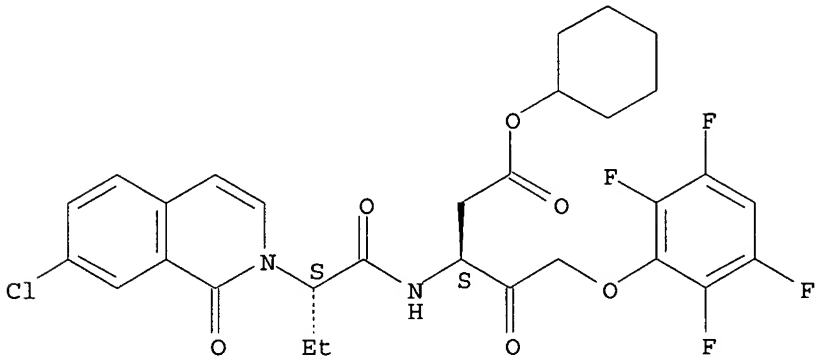
RN 721397-99-5 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(6,7-dichloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



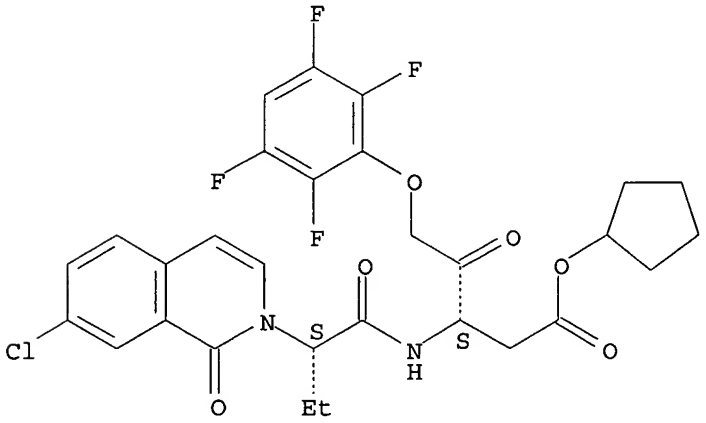
RN 721398-00-1 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cyclohexyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



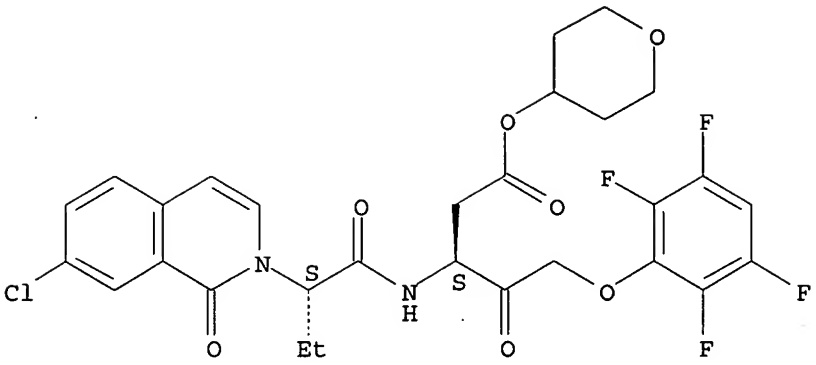
RN 721398-01-2 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cyclopentyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



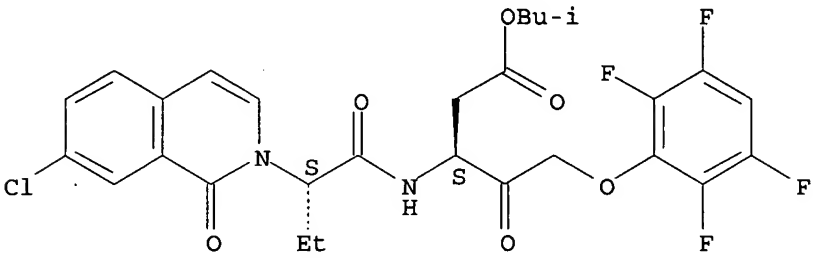
RN 721398-02-3 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, tetrahydro-2H-pyran-4-yl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



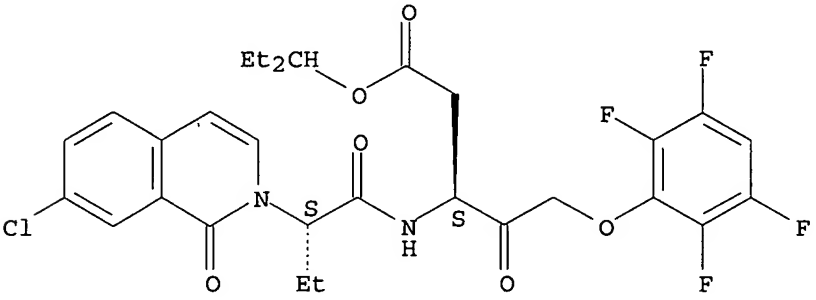
RN 721398-03-4 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 2-methylpropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



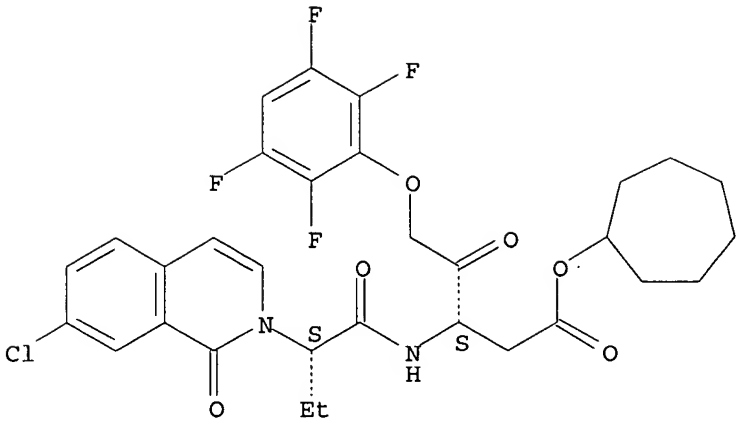
RN 721398-04-5 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-ethylpropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



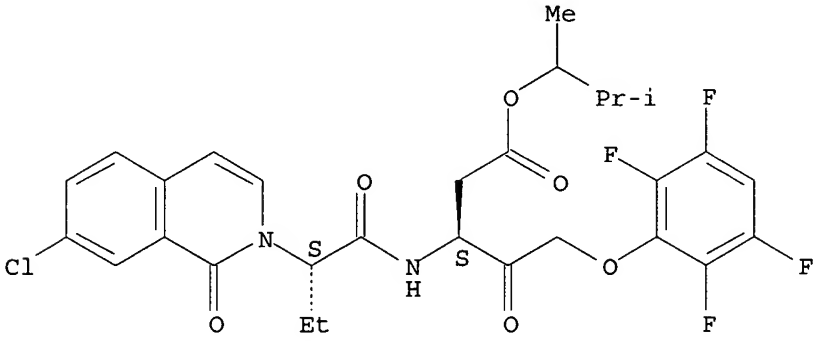
RN 721398-05-6 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cycloheptyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



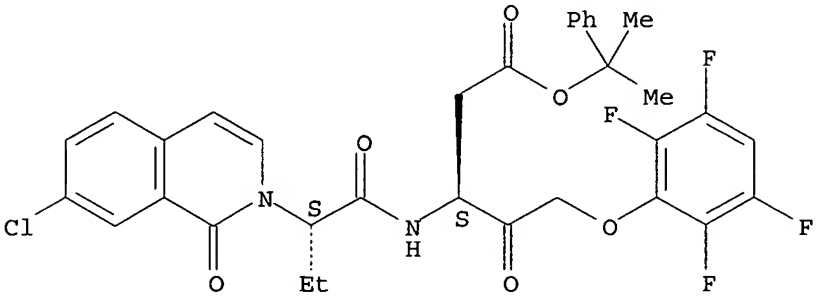
RN 721398-06-7 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,2-dimethylpropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 721398-07-8 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-methyl-1-phenylethyl ester, (3S)- (9CI) (CA INDEX NAME)

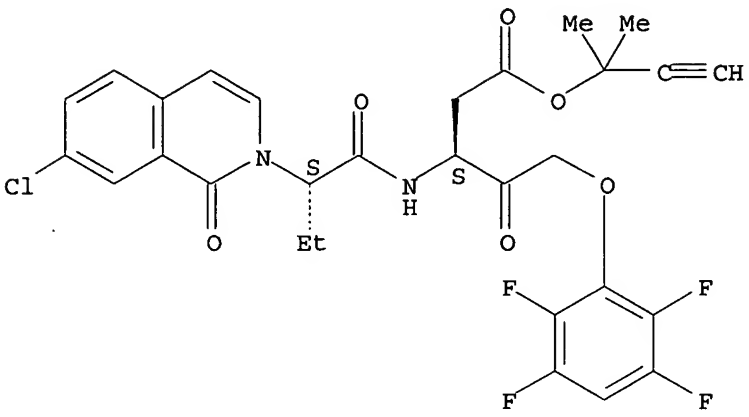
Absolute stereochemistry.



RN 721398-08-9 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-,

1,1-dimethyl-2-propynyl ester, (3S)- (9CI) (CA INDEX NAME)

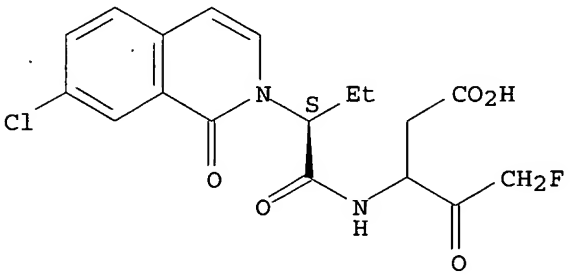
Absolute stereochemistry.



IT **618459-84-0P 640286-42-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

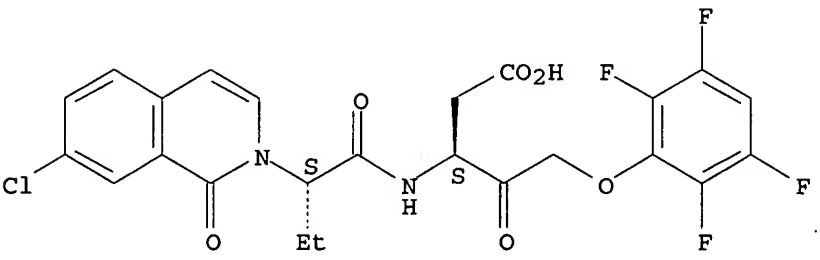
RN 618459-84-0 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 640286-42-6 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

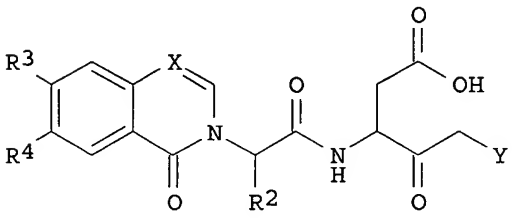
Absolute stereochemistry.



L19 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 2
ACCESSION NUMBER: 2004:20662 CAPLUS
DOCUMENT NUMBER: 140:77410
TITLE: Preparation of isoquinolinone and quinazolinone peptide derivatives as caspase inhibitors
INVENTOR(S): Knegtel, Ronald; Mortimore, Michael; Studley, John; Millan, David
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004002961	A1	20040108	WO 2003-US20557	20030627
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004072850	A1	20040415	US 2003-609147	20030627
PRIORITY APPLN. INFO.:			US 2002-392592P P	20020628
			US 2002-435073P P	20021220

OTHER SOURCE(S): MARPAT 140:77410
ED Entered STN: 11 Jan 2004
GI



I

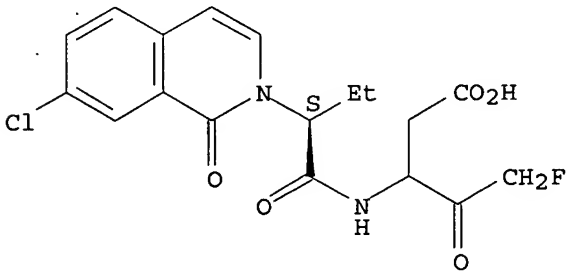
AB The invention relates to isoquinolinones and quinazolinones I [X is CH or N; Y is halo, tri- or tetrafluorophenoxy; R2 is alkyl; R3 is H, halo, OCF3, CN, or CF3; R4 is groups R3 or alkylthio, (un)substituted Ph, phenoxy, or phenylthio; with the proviso that when Y is halo, then R3 and R4 are not both H] which are caspase inhibitors useful in compns. for the treatment of various diseases, conditions, or disorders. Thus, I (X = CH, Y = F, R2 = Et, R3 = H, R4 = Cl), prepared by coupling of (S)-2-(7-chloro-1-oxo-1H-isoquinolin-2-yl)butyric acid (preparation given) with 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester, had Ki (M-1 s-1) > 500,000 for inhibition of caspase-1 or caspase-3, Ki 100,000-500,000 for

inhibition of caspase-8, and IC50 < 1 μM for inhibition of interleukin-1β secretion.

IT **618459-84-0P 618460-05-2P 618460-11-0P 618460-12-1P 640286-34-6P 640286-35-7P 640286-42-6P 640286-43-7P 640286-48-2P 640286-49-3P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of isoquinolinone and quinazolinone peptide derivs. as caspase inhibitors)

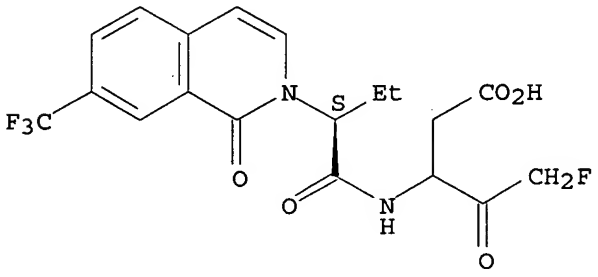
RN 618459-84-0 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 618460-05-2 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

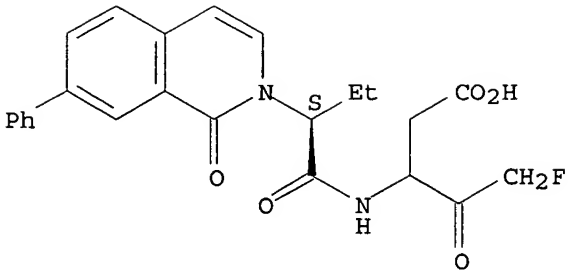
Absolute stereochemistry.



elected species

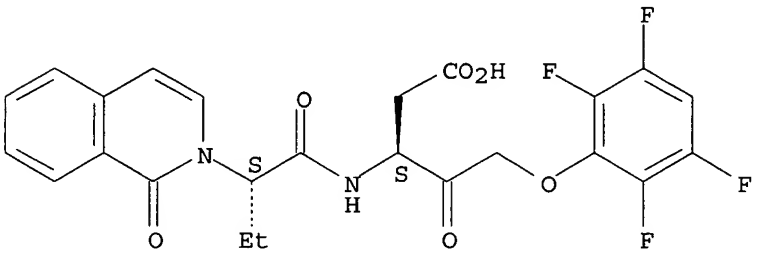
RN 618460-11-0 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-7-phenyl-2(1H)-isoquinolinyl)butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



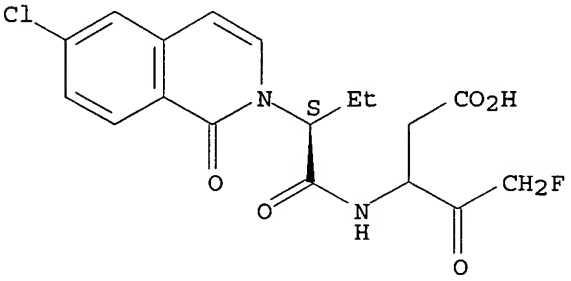
RN 618460-12-1 CAPLUS
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



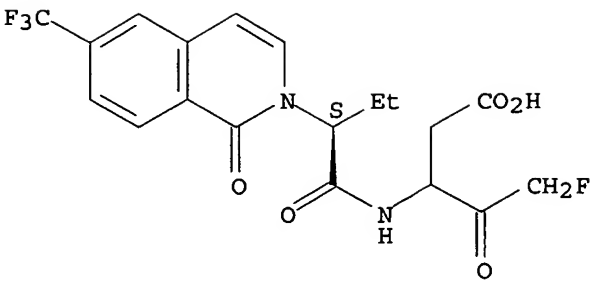
RN 640286-34-6 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(6-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 640286-35-7 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-6-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

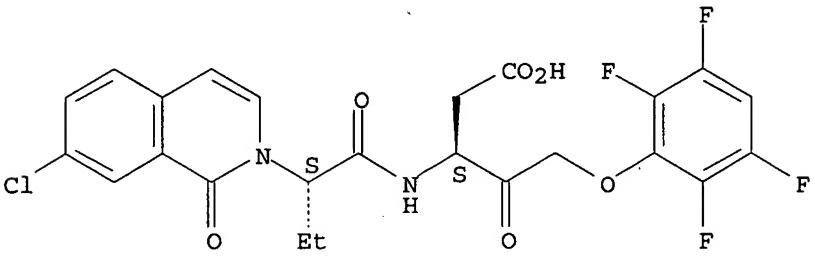
Absolute stereochemistry.



elected species

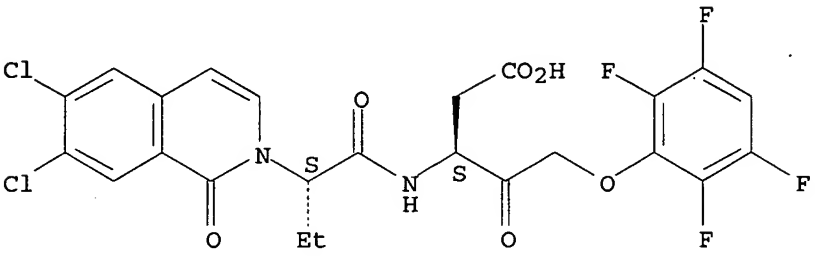
RN 640286-42-6 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



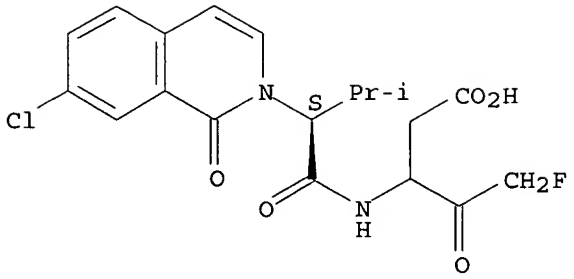
RN 640286-43-7 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(6,7-dichloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



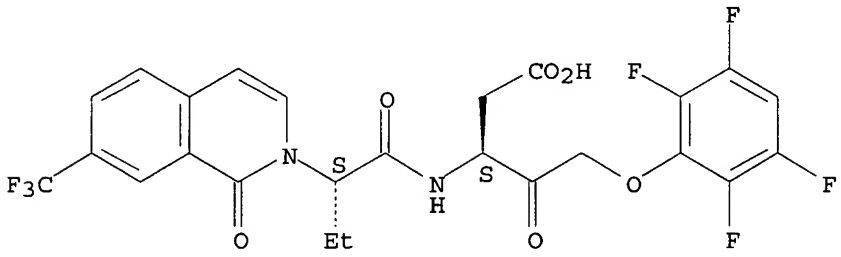
RN 640286-48-2 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-3-methyl-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



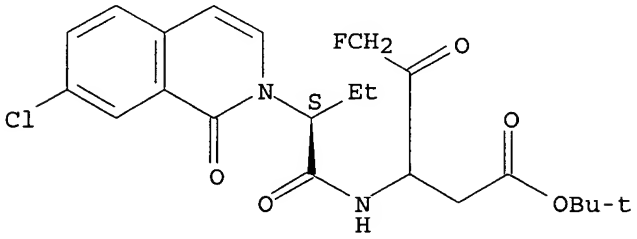
RN 640286-49-3 CAPLUS
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **640286-59-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of isoquinolinone and quinazolinone peptide derivs. as caspase inhibitors)
RN 640286-59-5 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

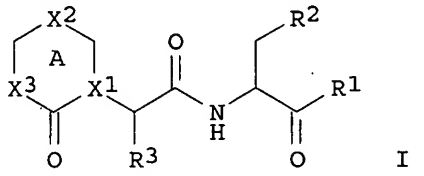
L19 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:991174 CAPLUS
DOCUMENT NUMBER: 140:28050
TITLE: Synthesis of peptide heterocyclic derivatives as caspase inhibitors

INVENTOR(S): Golec, Julian M. C.; Charifson, Paul S.; Charrier, Jean-Damien; Binch, Hayley
PATENT ASSIGNEE(S): UK
SOURCE: U.S. Pat. Appl. Publ., 28 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

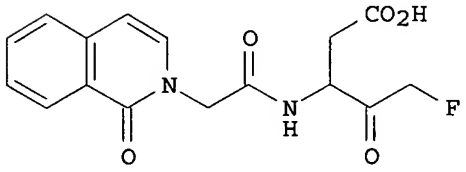
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003232846	A1	20031218	US 2002-166437	20020610
PRIORITY APPLN. INFO.:			US 2002-166437	20020610

OTHER SOURCE(S): MARPAT 140:28050
ED Entered STN: 21 Dec 2003
GI

not patent



I

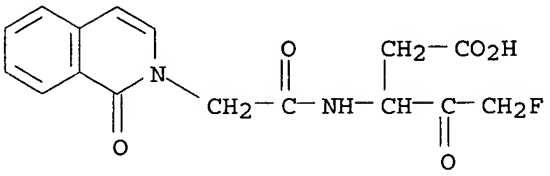


II

AB Compds. I and their synthesis are claimed [R1 = H, CN, CHN2, (substituted)alkyl, aryl, non-aromatic heterocycle, etc.; R2 = CH2COOH, CO2H (or ester/amide/isosteres of); R3 = H or alkyl; X1, X3 = N or C; X2 = bond, O, S, N or C wherein any X with suitable valence may bear a substituent; each C in ring A may also be substituted; ring A substituents = H, halo, alkyl, aryl, OH, CN, etc.; A may also bear a fused ring]. Over 20 synthetic examples are given. Thus, substitution of bromoacetic acid Et ester with the corresponding isoquinolone followed by saponification and coupling to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester provided the hydroxy ester intermediate. Oxidation of the hydroxy ester followed by treatment with TFA yielded II as a white powder. Compds. of the invention are caspase inhibitors; data is provided for caspase-1,-3,-7 and caspase-8 inhibition (Ki). Also determined was inhibition of IL-1β secretion from peripheral blood mononuclear cells and activity in a Fas ligand induced apoptosis assay. Compound II had Ki (M-1 s-1) of 248,000 for caspase-1, 130,000 for caspase-3 and an IC50 of 2.9 μM for IL-1β secretion. Compds. I may be used as a component of immunotherapy for the treatment of cancer.

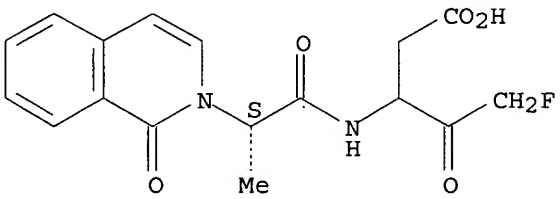
IT **344461-02-5P 344461-03-6P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis of peptide heterocyclic derivs. as caspase inhibitors)
RN 344461-02-5 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(1-oxo-2(1H)-isoquinolinyl)acetyl]amino]- (9CI) (CA INDEX NAME)



RN 344461-03-6 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

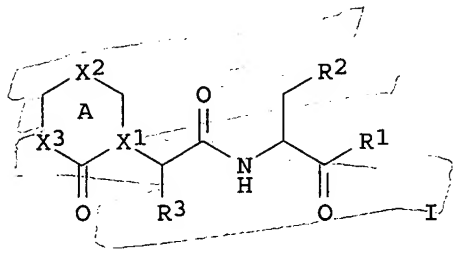


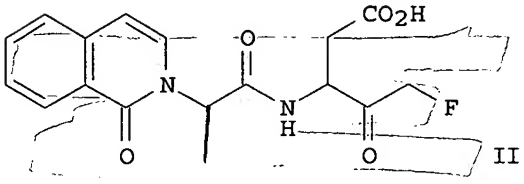
L19 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2001:435047 CAPLUS
DOCUMENT NUMBER: 135:46192
TITLE: Synthesis and use of heterocyclic substituted-amido halopentanoate derivatives as caspase inhibitors
INVENTOR(S): Golec, Julian; Charifson, Paul; Charrier, Jean-Damien; Binch, Hayley
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001042216	A2	20010614	WO 2000-US33260	20001208
WO 2001042216	A3	20020228		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2393710	AA	20010614	CA 2000-2393710	20001208
BR 2000016282	A	20020827	BR 2000-16282	20001208
EP 1244626	A2	20021002	EP 2000-988026	20001208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003516393	T2	20030513	JP 2001-543517	20001208

NZ 519424	A	20040326	NZ 2000-519424		20001208
ZA 2002004390	A	20030602	ZA 2002-4390		20020531
NO 2002002656	A	20020806	NO 2002-2656		20020605
PRIORITY APPLN. INFO.:			US 1999-169812P	P	19991208
			WO 2000-US33260	W	20001208

OTHER SOURCE(S): MARPAT 135:46192
ED Entered STN: 15 Jun 2001
GI



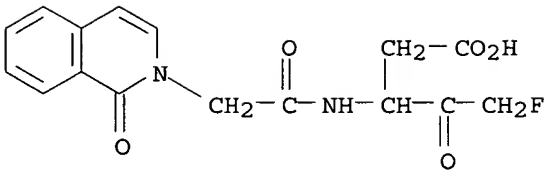


AB Compds. I and their synthesis are claimed [wherein; R1 = H, CN, CHN2, (substituted)alkyl, aryl, non-aromatic heterocycle, etc.; R2 = CH2COOH, COOH (or ester/amide/isosteres of); R3 = H or alkyl; X1, X3 = N or C; X2 = bond, O, S, N or C wherein any X with suitable valence may bear a substituent; each C in ring A may also be substituted; ring A substituents = H, halo, alkyl, aryl, OH, CN, etc.; A may also bear a fused ring]. Over 20 synthetic examples are given. For instance; substitution of bromoacetic acid Et ester with the corresponding isoquinolone followed by saponification and coupling to 3-amino-5-fluoro-4-hydroxypentanoic acid tert-Bu ester provided the hydroxy ester intermediate. Oxidation of the hydroxy ester followed by treatment with TFA yielded II as a white powder. Compds. of the invention are caspase inhibitors; data is provided for caspase-1,-3,-7 and caspase-8 inhibition (Ki). Also determined was inhibition of IL-1β secretion from peripheral blood mononuclear cells and activity in a Fas ligand induced apoptosis assay. Compound II had Ki (M-1 s-1) of 248,000 for caspase-1, 130,000 for caspase-3 and an IC50 of 2.9 μM for IL-1β secretion. Compds. I may be used as a component of immunotherapy for the treatment of cancer.

IT **344461-02-5P 344461-03-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and use of heterocyclic substituted-amido halopentanoate derivs. as caspase inhibitors)

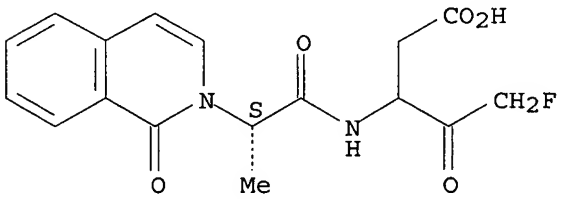
RN 344461-02-5 CAPLUS

CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(1-oxo-2(1H)-isoquinolinyl)acetyl]amino]- (9CI) (CA INDEX NAME)



RN 344461-03-6 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:855766 CAPLUS
DOCUMENT NUMBER: 139:345913
TITLE: Identification of tumor necrosis factor α (TNF-α) modulator compounds, and use for treatment of TNF-mediated diseases
INVENTOR(S): Miller, Karen; Diu-Hercend, Anita; Hercend, Thierry; Lang, Paul; Weber, Peter; Golec, Julian; Mortimore, Michael
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 268 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

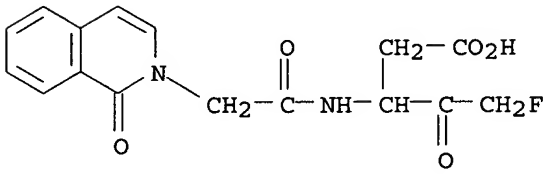
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003088917	A2	20031030	WO 2003-US12262	20030417
WO 2003088917	A3	20040304		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004048797	A1	20040311	US 2003-419327	20030417
PRIORITY APPLN. INFO.:			US 2002-374434P P	20020419

ED Entered STN: 31 Oct 2003
AB The invention discloses methods for identifying compds. useful for regulating TNF-α levels and/or activity. The invention also discloses methods for decreasing TNF-α levels and/or activity.

Compds. and compns. of the invention are useful for treating TNF-mediated diseases. The invention further discloses kits comprising the compds. and compns. herein and a tool for measuring TNF-α activity and/or levels. Preparation of selected compds., e.g. [3S/R,(2S)]-5-fluoro-4-oxo-3-[(1-(phenothiazine-10-carbonyl)piperidine-2-carbonyl)amino]pentanoic acid, is described.

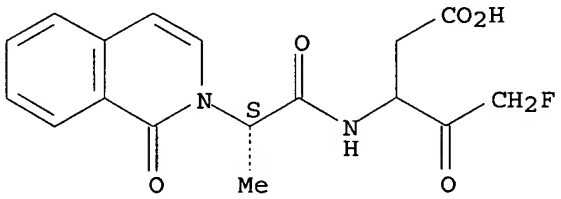
IT **344461-02-5 344461-03-6 618459-84-0**
618459-95-3 618460-05-2 618460-08-5
618460-10-9 618460-11-0 618460-12-1
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(TNF-α modulator compound identification methods, and use for treatment of TNF-mediated diseases)

RN 344461-02-5 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(1-oxo-2(1H)-isoquinolinyl)acetyl]amino]- (9CI) (CA INDEX NAME)



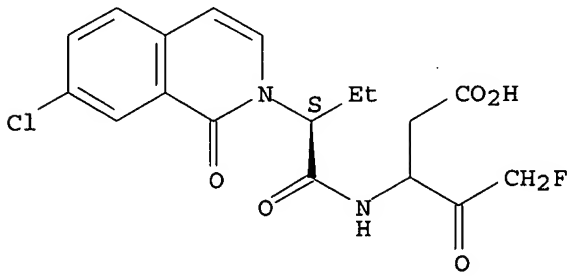
RN 344461-03-6 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



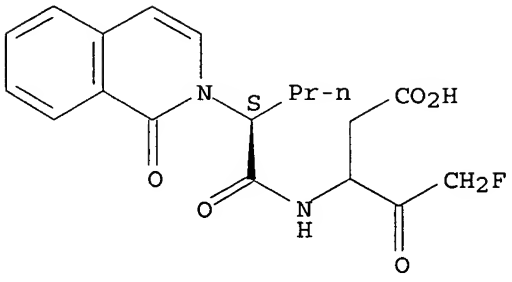
RN 618459-84-0 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



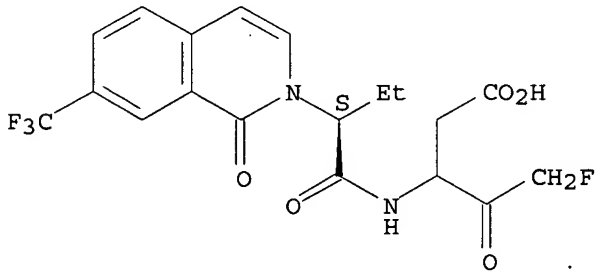
RN 618459-95-3 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)pentyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



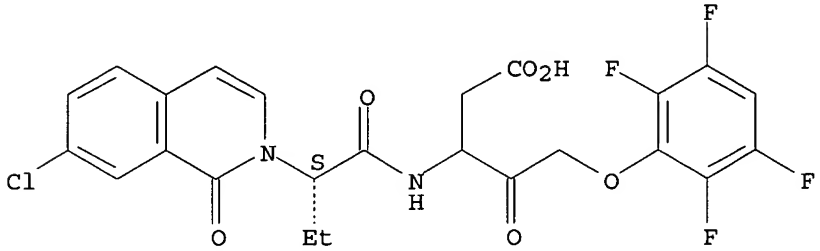
RN 618460-05-2 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 618460-08-5 CAPLUS
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

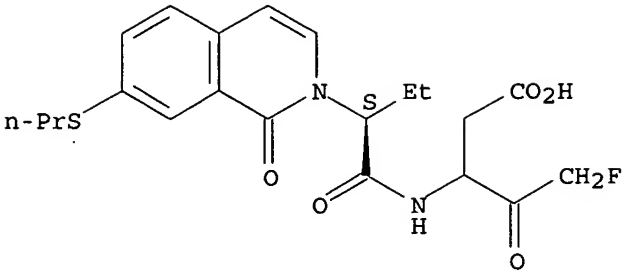


RN 618460-10-9 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(propylthio)-2(1H)-isoquinolinyl]butyl]amino]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

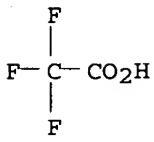
CRN 618460-09-6
CMF C21 H25 F N2 O5 S

Absolute stereochemistry.



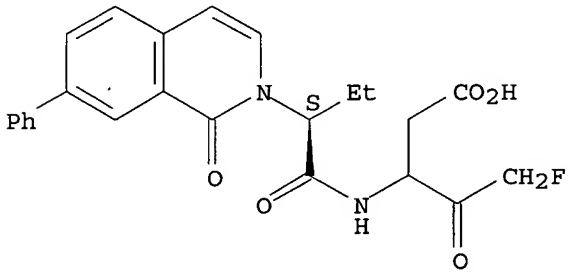
CM 2

CRN 76-05-1
CMF C2 H F3 O2



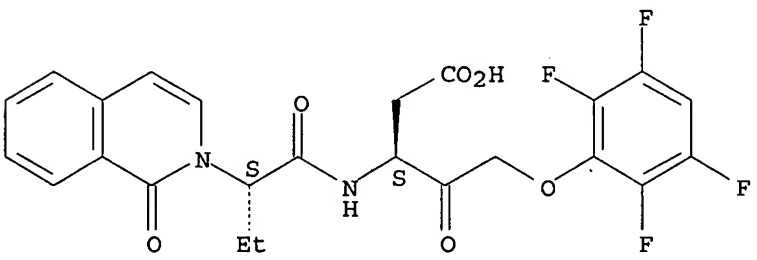
RN 618460-11-0 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-7-phenyl-2(1H)-isoquinolinyl)butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 618460-12-1 CAPLUS
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

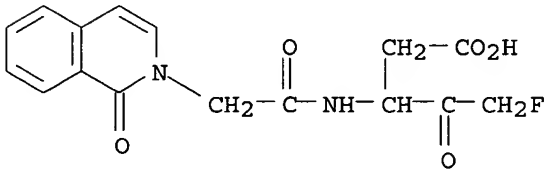
Absolute stereochemistry.



L19 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:656594 CAPLUS
DOCUMENT NUMBER: 139:191460
TITLE: Phospholipids as caspase inhibitor prodrugs
INVENTOR(S): Mortimore, Michael; Golec, Julian M. C.
PATENT ASSIGNEE(S): Vertex Pharmaceuticals Incorporated, USA
SOURCE: PCT Int. Appl., 256 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

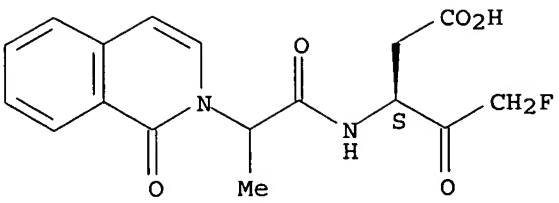
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003068242	A1	20030821	WO 2003-US4457	20030211
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004019017	A1	20040129	US 2003-366192	20030211
PRIORITY APPLN. INFO.:			US 2002-355889P P	20020211

OTHER SOURCE(S): MARPAT 139:191460
ED Entered STN: 22 Aug 2003
AB The invention relates to compds. which are prodrugs of caspase inhibitors and pharmaceutically acceptable salts thereof. The invention further relates to the release of caspase inhibitors from these compds. through selective bond cleavage. The invention further relates to pharmaceutical compns. comprising these compds., which are particularly well-suited for treatment of caspase-mediated diseases, including inflammatory and degenerative diseases. The invention further relates to methods for preparing compds. of this invention.
IT **344461-02-5 582317-55-3**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phospholipids as caspase inhibitor prodrugs)
RN 344461-02-5 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(1-oxo-2(1H)-isoquinolinyl)acetyl]amino]- (9CI) (CA INDEX NAME)



RN 582317-55-3 CAPLUS
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 7 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2004:248012 USPATFULL
TITLE: Caspase inhibitors and uses thereof
INVENTOR(S): Charrier, Jean-Damien, Wantage, UNITED KINGDOM
Mortimore, Michael, Burford, UNITED KINGDOM
Studley, John R., Abingdon, UNITED KINGDOM

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004192612	A1	20040930	
APPLICATION INFO.:	US 2003-743563	A1	20031222	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-435133P	20021220	(60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: VERTEX PHARMACEUTICALS INC., 130 WAVERLY STREET, CAMBRIDGE, MA, 02139-4242
NUMBER OF CLAIMS: 38
EXEMPLARY CLAIM: 1
LINE COUNT: 1873
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides a compound of formula I: ##STR1##

wherein:

X is --OR.sup.1 or --N(R.sup.5).sub.2,

Y is halo, trifluorophenoxy, or tetrafluorophenoxy;

R.sup.1 is:

C.sub.1-6 straight chained or branched alkyl, alkenyl, or alkynyl, wherein the alkyl, alkenyl, or alkynyl is optionally substituted with optionally substituted aryl, CF.sub.3, Cl, F, OMe, OEt, OCF.sub.3, CN, or NMe.sub.2;

C.sub.1-6 cycloalkyl, wherein 1-2 carbon atoms in the cycloalkyl is optionally replaced with --O-- or --NR.sup.5--;

R.sup.2 is C.sub.1-6 straight chained or branched alkyl;

R.sup.3 is hydrogen, halo, OCF.sub.3, CN, or CF.sub.3;

R.sup.4 is hydrogen, halo, OCF.sub.3, CN, or CF.sub.3; and

each R.sup.5 is independently H, C.sub.1-6 straight chained or branched alkyl, aryl, --O--C.sub.1-6 straight chained or branched alkyl, or

--O-aryl.

The present invention also provides pharmaceutical compositions and methods using such compositions for treating a caspase-mediated disease, particularly in the central nervous system.

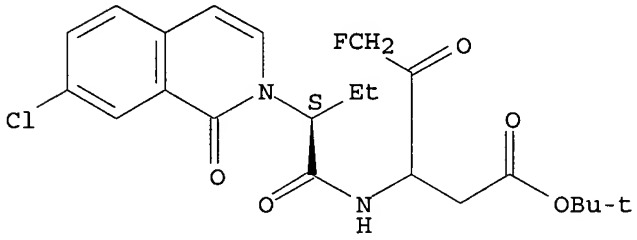
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT **640286-59-5P 721397-83-7P**
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

RN 640286-59-5 USPATFULL

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

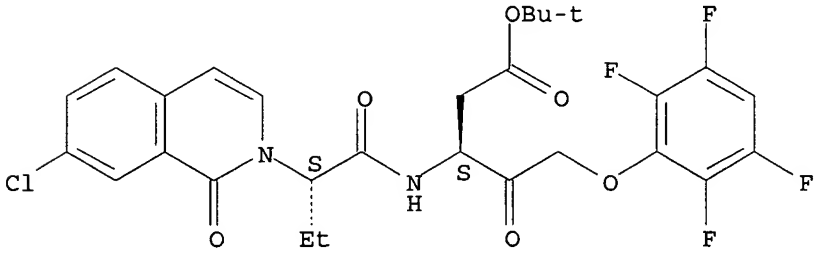
Absolute stereochemistry.



RN 721397-83-7 USPATFULL

CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

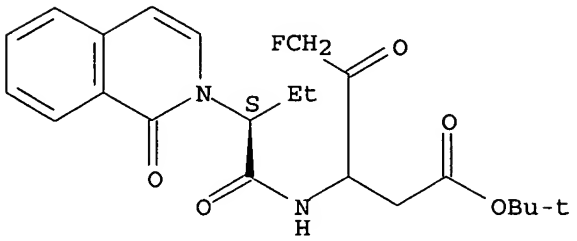


IT **721397-79-1P 721397-80-4P 721397-81-5P**
721397-82-6P 721397-84-8P 721397-85-9P
721397-86-0P 721397-87-1P 721397-88-2P
721397-89-3P 721397-90-6P 721397-91-7P
721397-92-8P 721397-93-9P 721397-94-0P
721397-95-1P 721397-96-2P 721397-97-3P
721397-98-4P 721397-99-5P 721398-00-1P
721398-01-2P 721398-02-3P 721398-03-4P
721398-04-5P 721398-05-6P 721398-06-7P
721398-07-8P 721398-08-9P
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)

RN 721397-79-1 USPATFULL

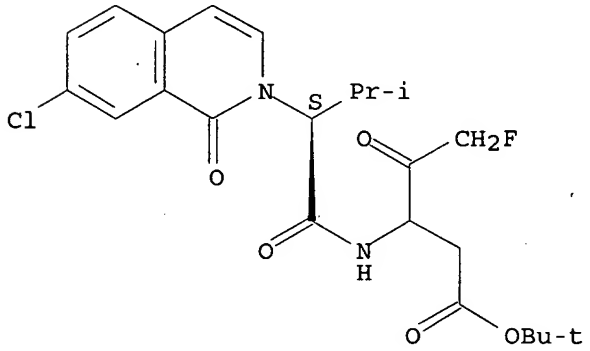
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



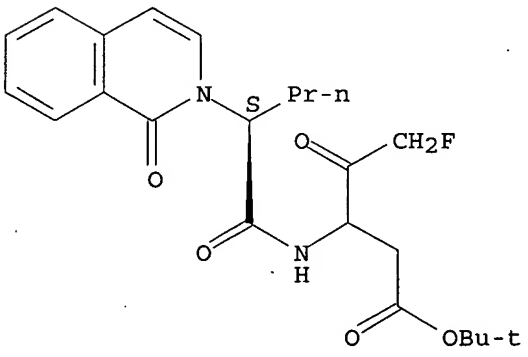
RN 721397-80-4 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-3-methyl-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



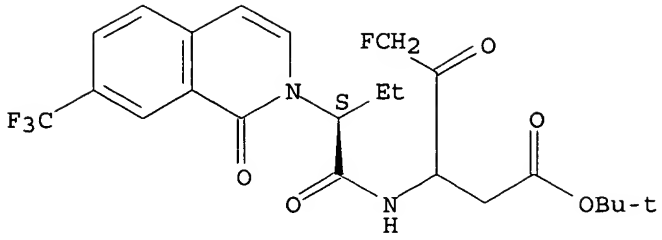
RN 721397-81-5 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)pentyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



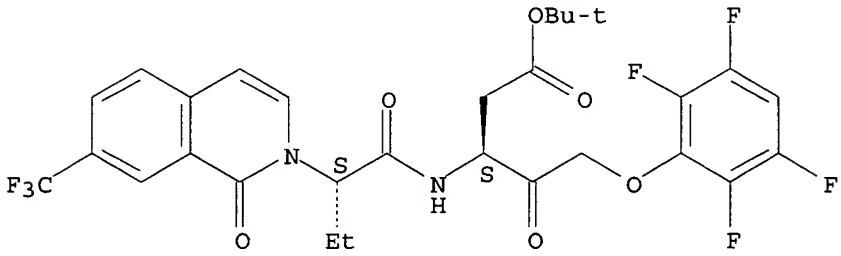
RN 721397-82-6 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



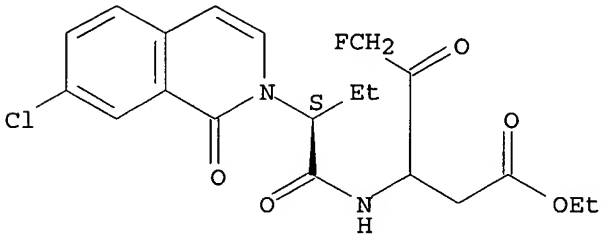
RN 721397-84-8 USPATFULL
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



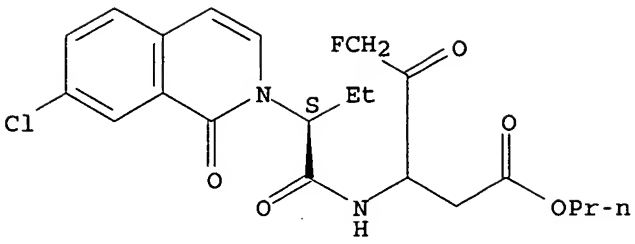
RN 721397-85-9 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



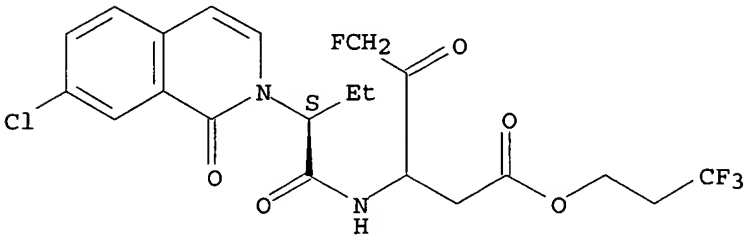
RN 721397-86-0 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, propyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



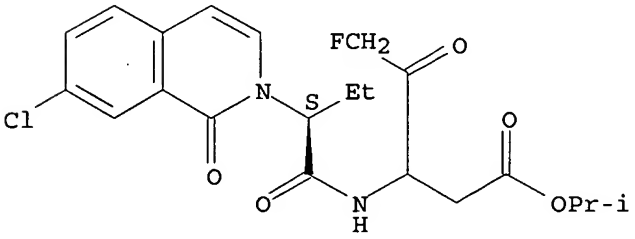
RN 721397-87-1 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 3,3,3-trifluoropropyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



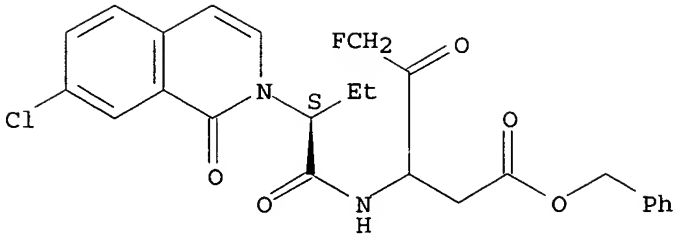
RN 721397-88-2 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1-methylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



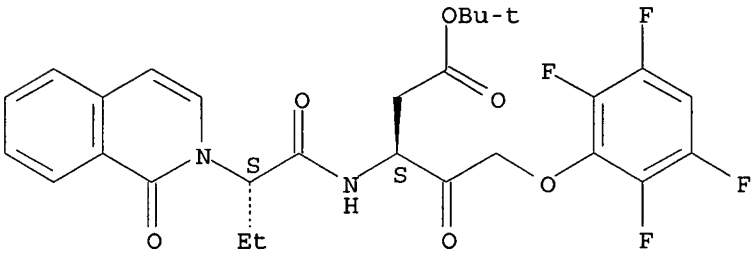
RN 721397-89-3 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, phenylmethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



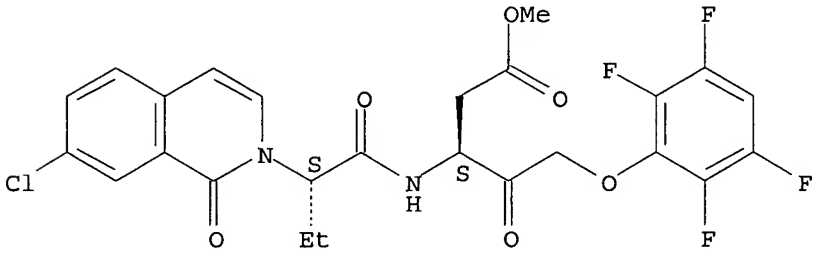
RN 721397-90-6 USPATFULL
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



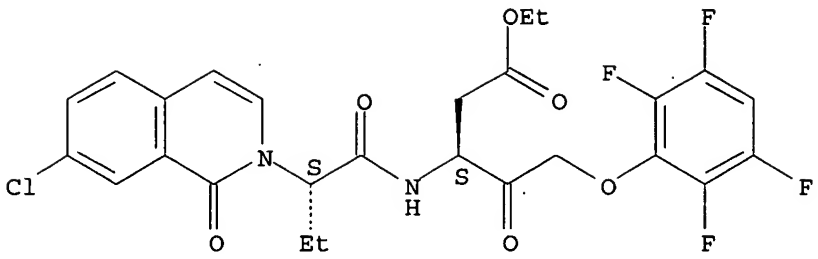
RN 721397-91-7 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, methyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



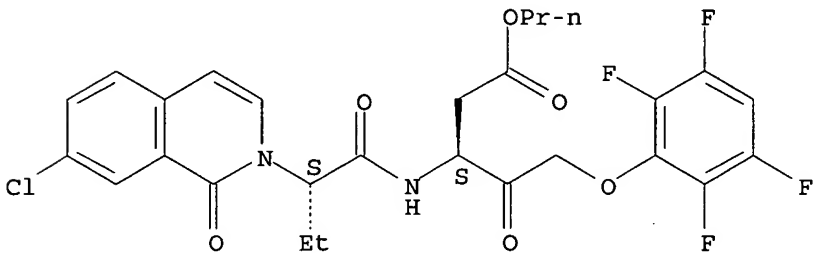
RN 721397-92-8 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, ethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



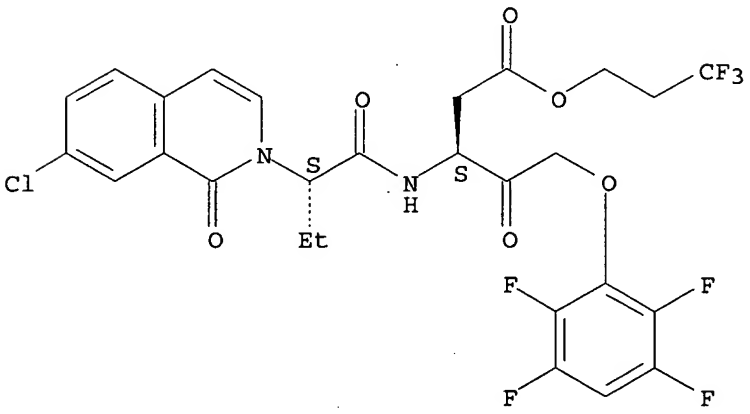
RN 721397-93-9 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, propyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



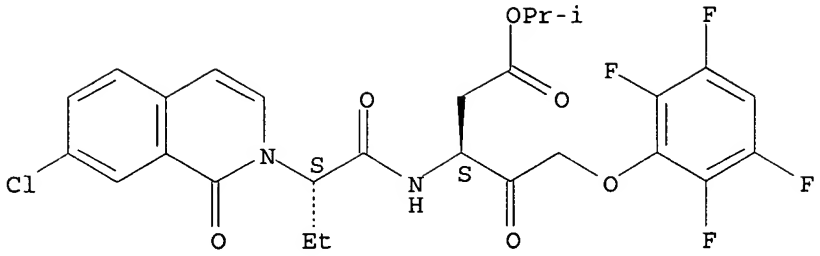
RN 721397-94-0 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 3,3,3-trifluoropropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



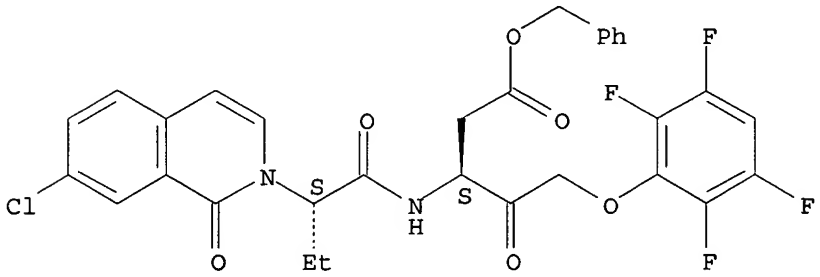
RN 721397-95-1 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-methylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



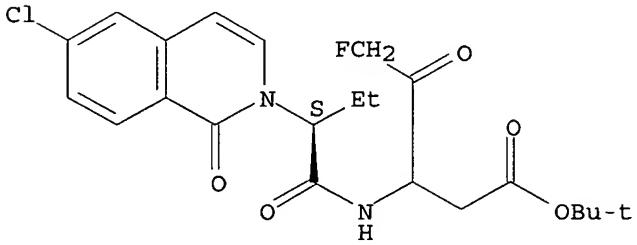
RN 721397-96-2 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, phenylmethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



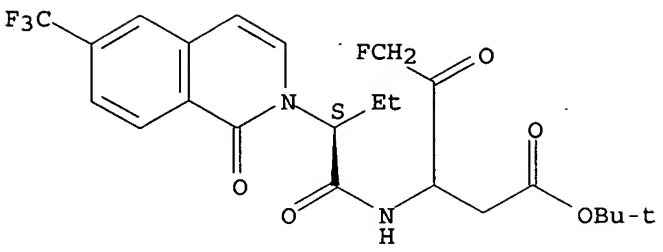
RN 721397-97-3 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(6-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 721397-98-4 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-6-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

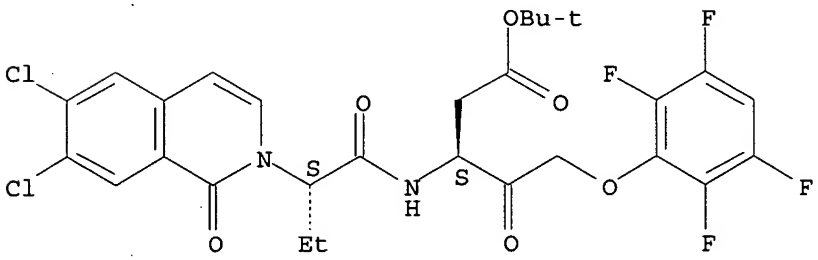
Absolute stereochemistry.



t-butyl ester of elected species

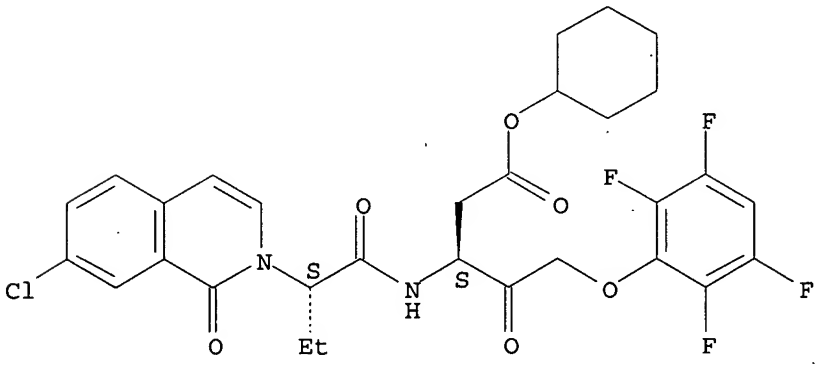
RN 721397-99-5 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(6,7-dichloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



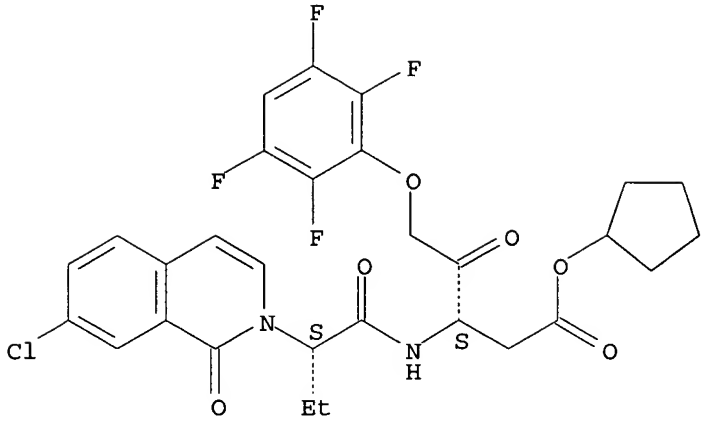
RN 721398-00-1 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cyclohexyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



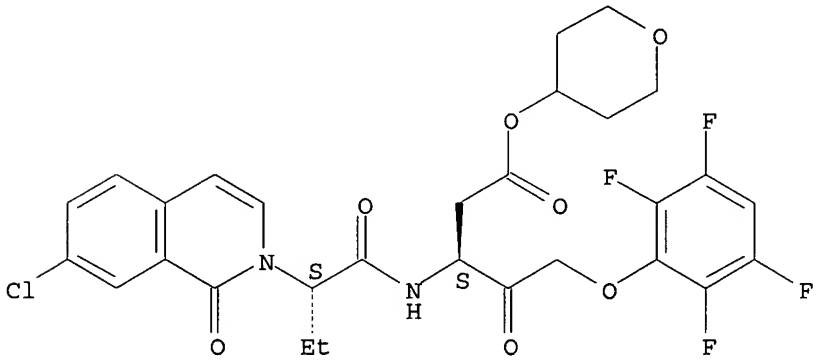
RN 721398-01-2 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cyclopentyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



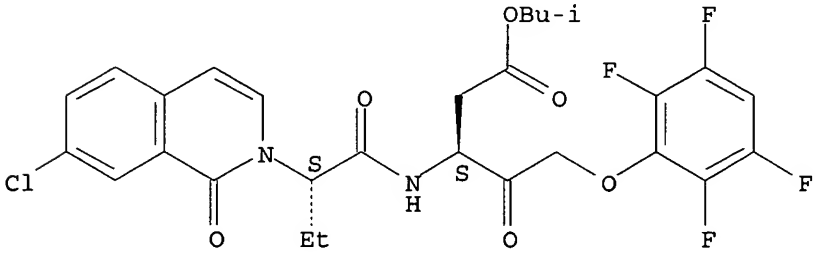
RN 721398-02-3 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, tetrahydro-2H-pyran-4-yl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



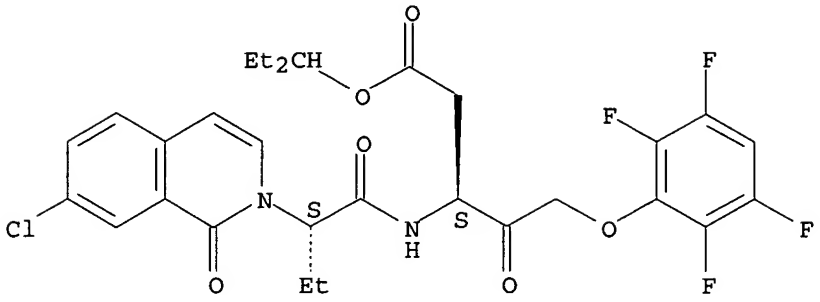
RN 721398-03-4 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 2-methylpropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



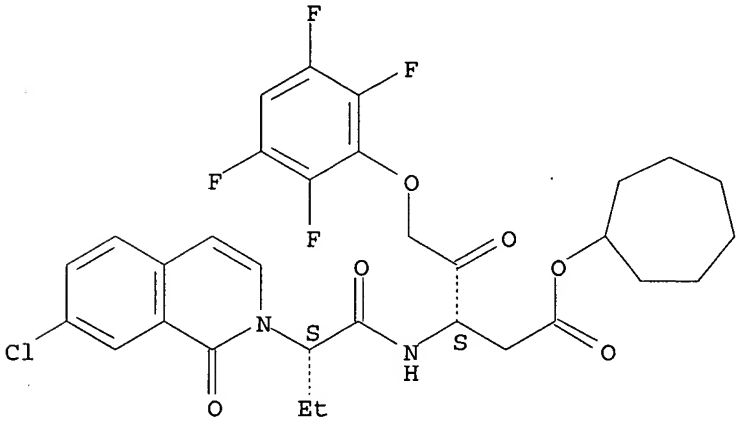
RN 721398-04-5 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-ethylpropyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



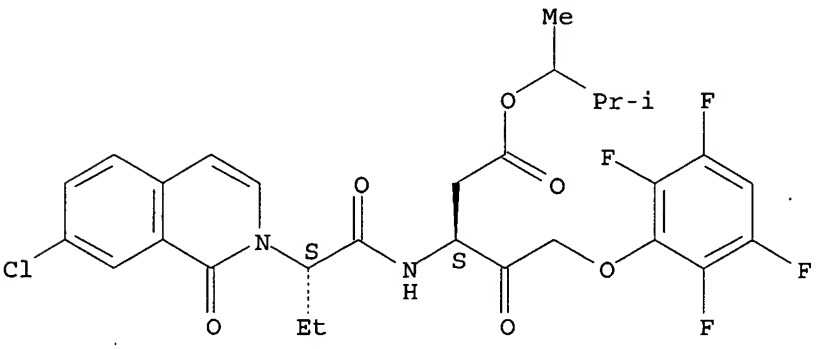
RN 721398-05-6 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, cycloheptyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 721398-06-7 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,2-dimethylpropyl ester, (3S)- (9CI) (CA INDEX NAME)

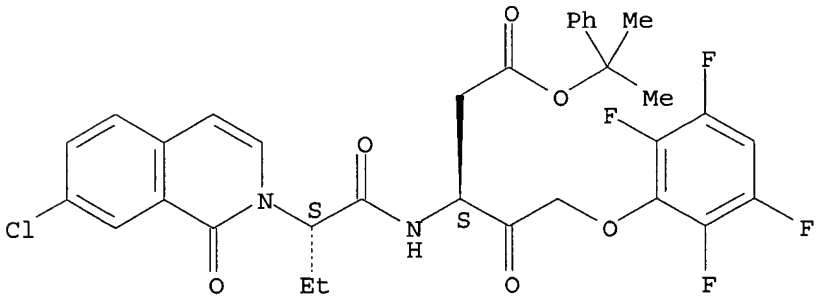
Absolute stereochemistry.



RN 721398-07-8 USPATFULL

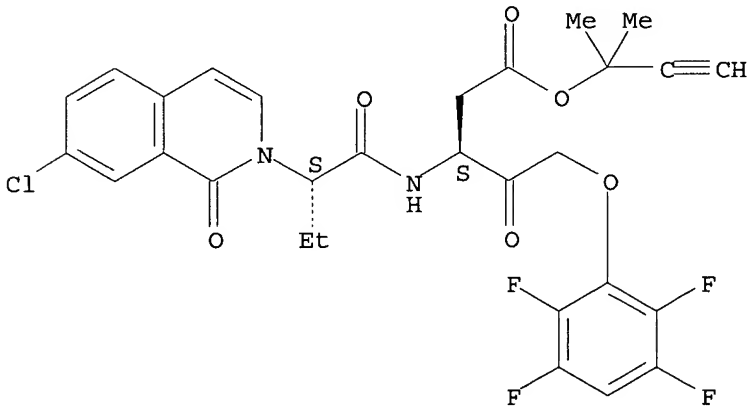
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1-methyl-1-phenylethyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



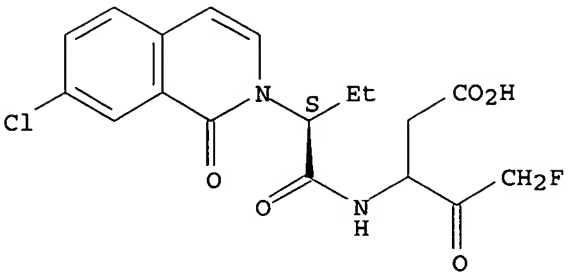
RN 721398-08-9 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, 1,1-dimethyl-2-propynyl ester, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



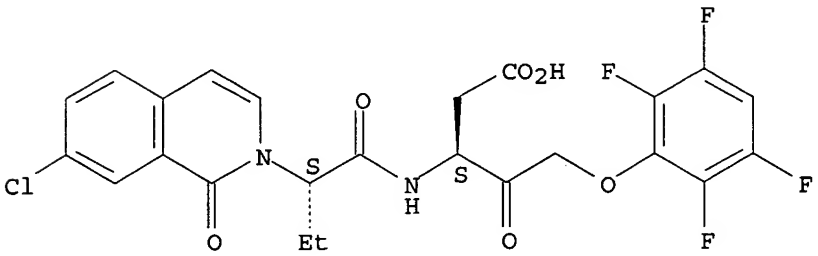
IT **618459-84-0P 640286-42-6P**
(preparation of (oxoisoquinolinylacetylamino)-oxopentanoic acid ester and amide derivs. as caspase inhibitors)
RN 618459-84-0 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 640286-42-6 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 8 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2004:95395 USPATFULL
TITLE: Caspase inhibitors and uses thereof
INVENTOR(S): Knegtel, Ronald, Abingdon, UNITED KINGDOM
Mortimore, Michael, Burford, UNITED KINGDOM
Studley, John, Abingdon, UNITED KINGDOM
Millan, David, Abingdon, UNITED KINGDOM

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004072850	A1	20040415	
APPLICATION INFO.:	US 2003-609147	A1	20030627	(10)

	NUMBER	DATE	
PRIORITY INFORMATION:	US 2002-392592P	20020628	(60)
	US 2002-435073P	20021220	(60)

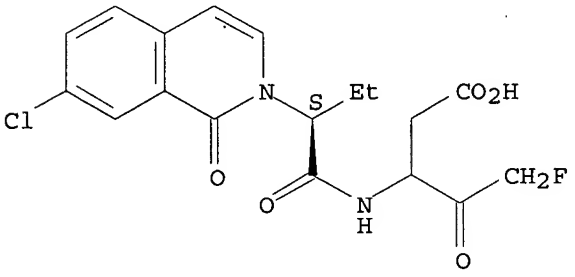
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: VERTEX PHARMACEUTICALS INC., 130 WAVERLY STREET, CAMBRIDGE, MA, 02139-4242
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
LINE COUNT: 1898
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to compounds of formula I: ##STR1##

useful as inhibitors of caspases. The present invention also provides pharmaceutically acceptable compositions comprising said compounds, processes for preparing the compounds, and methods of using the

compounds and compositions in the treatment of various diseases, conditions, or disorders.

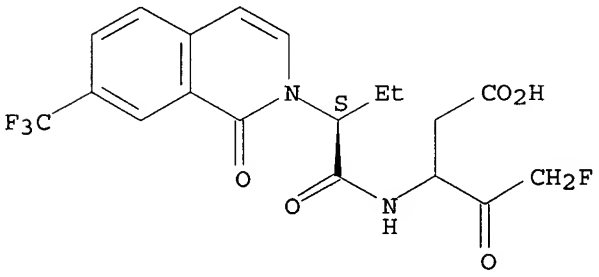
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **618459-84-0P 618460-05-2P 618460-11-0P 618460-12-1P 640286-34-6P 640286-35-7P 640286-42-6P 640286-43-7P 640286-48-2P 640286-49-3P**
(preparation of isoquinolinone and quinazolinone peptide derivs. as caspase inhibitors)
RN 618459-84-0 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



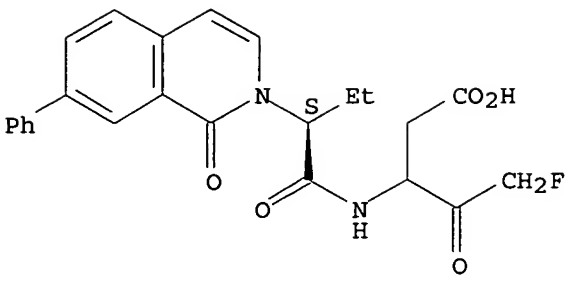
RN 618460-05-2 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



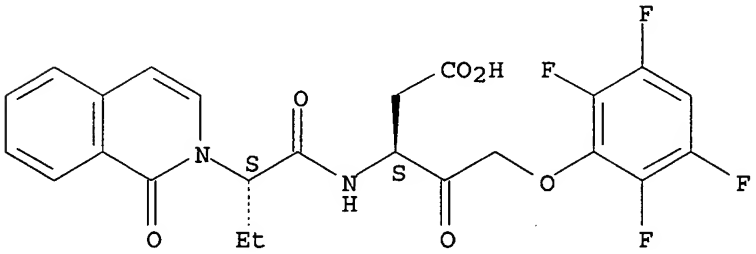
RN 618460-11-0 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-7-phenyl-2(1H)-isoquinolinyl)butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



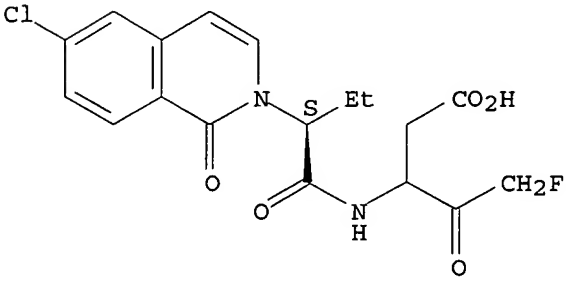
RN 618460-12-1 USPATFULL
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



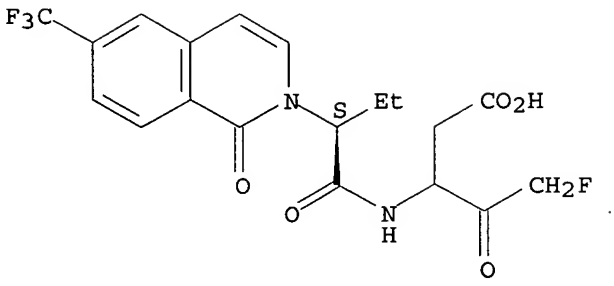
RN 640286-34-6 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(6-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



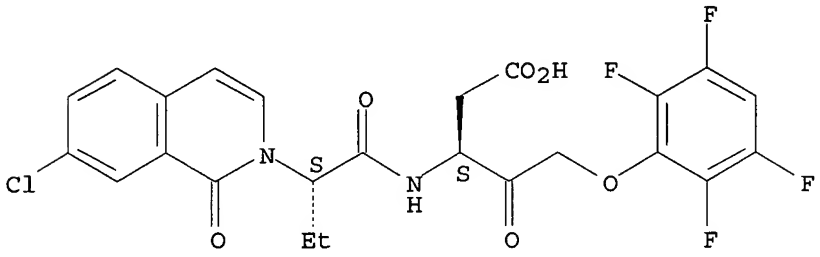
RN 640286-35-7 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-6-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



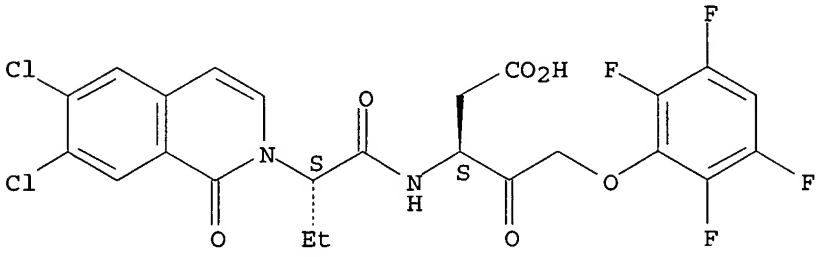
RN 640286-42-6 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



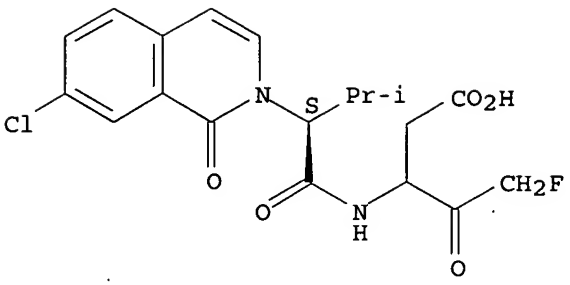
RN 640286-43-7 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(6,7-dichloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



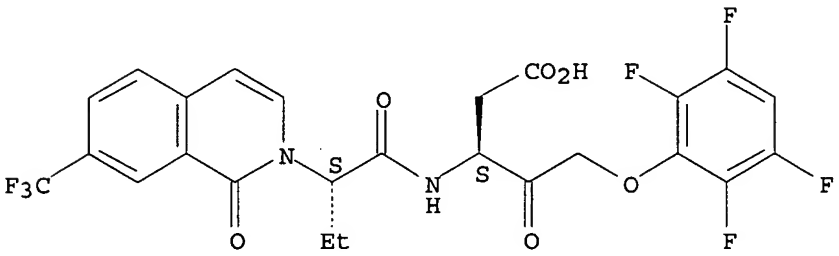
RN 640286-48-2 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-3-methyl-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



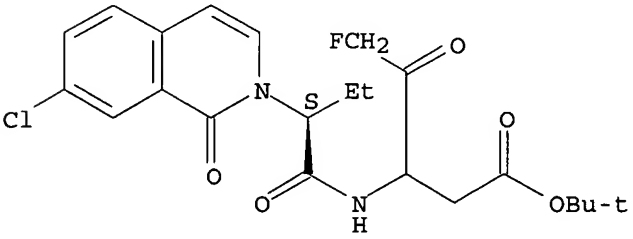
RN 640286-49-3 USPATFULL
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **640286-59-5P**
(preparation of isoquinolinone and quinazolinone peptide derivs. as caspase inhibitors)
RN 640286-59-5 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 9 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2004:64278 USPATFULL
TITLE: Regulation of TNF-alpha
INVENTOR(S): Miller, Karen, Newbury, UNITED KINGDOM
Diu-Hercend, Anita, Charenton le Pont, FRANCE
Hercend, Thierry, Charenton le Pont, FRANCE
Lang, Paul, Viuz-en-Sallaz, FRANCE
Weber, Peter, Abingdon, UNITED KINGDOM
Golec, Julian, Ashbury, UNITED KINGDOM

Mortimore, Michael, Burford, UNITED KINGDOM

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004048797	A1	20040311
APPLICATION INFO.:	US 2003-419327	A1	20030417 (10)

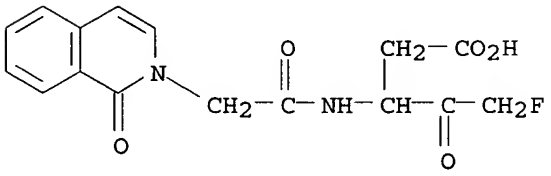
	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-374434P	20020419 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & NEAVE, 1251 AVENUE OF THE AMERICAS, 50TH FLOOR, NEW YORK, NY, 10020-1105
NUMBER OF CLAIMS: 9
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 210 Drawing Page(s)
LINE COUNT: 1320
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention relates to methods for identifying compounds useful for regulating TNF-alpha levels and/or activity. The invention also relates to methods for decreasing TNF-alpha levels and/or activity. Compounds and compositions according to this invention are useful for treating TNF-mediated diseases. The invention also relates to kits comprising the compounds and compositions herein and a tool for measuring TNF-alpha activity and/or levels.

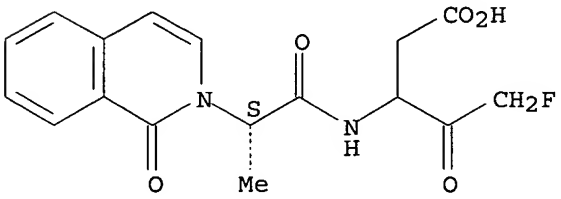
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **344461-02-5 344461-03-6 618459-84-0**
618459-95-3 618460-05-2 618460-08-5
618460-10-9 618460-11-0 618460-12-1
(TNF-α modulator compound identification methods, and use for treatment of TNF-mediated diseases)

RN 344461-02-5 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(1-oxo-2(1H)-isoquinolinyl)acetyl]amino]- (9CI) (CA INDEX NAME)



RN 344461-03-6 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]- (9CI) (CA INDEX NAME)

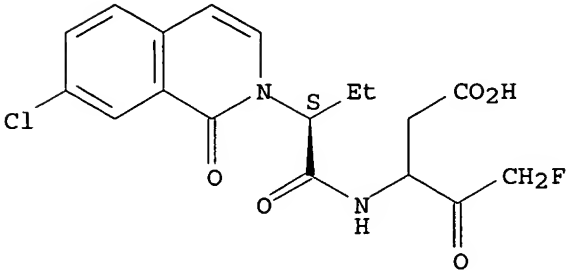
Absolute stereochemistry.



RN 618459-84-0 USPATFULL

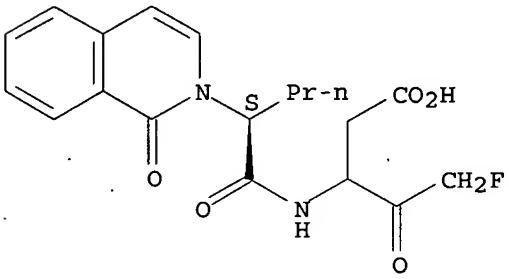
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-5-fluoro-4-oxo- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



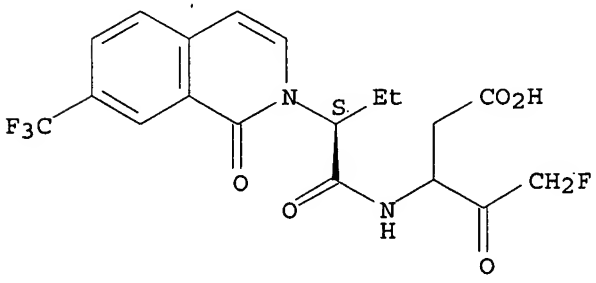
RN 618459-95-3 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)pentyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 618460-05-2 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(trifluoromethyl)-2(1H)-isoquinolinyl]butyl]amino]- (9CI) (CA INDEX NAME)

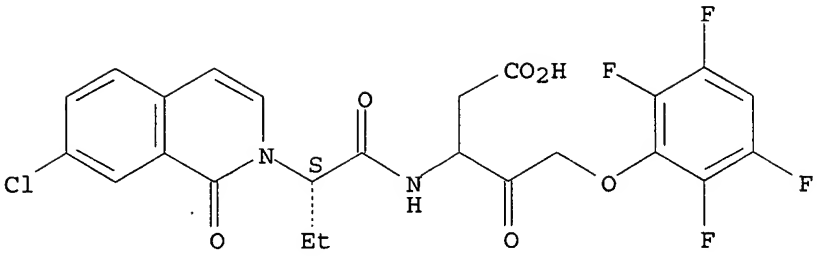
Absolute stereochemistry.



elected species

RN 618460-08-5 USPATFULL
CN Pentanoic acid, 3-[[(2S)-2-(7-chloro-1-oxo-2(1H)-isoquinolinyl)-1-oxobutyl]amino]-4-oxo-5-(2,3,5,6-tetrafluorophenoxy)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

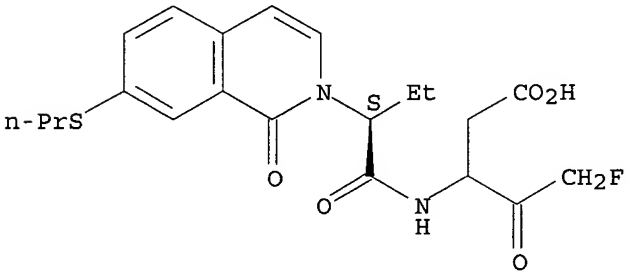


RN 618460-10-9 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-[1-oxo-7-(propylthio)-2(1H)-isoquinolinyl]butyl]amino]-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

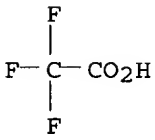
CRN 618460-09-6
CMF C21 H25 F N2 O5 S

Absolute stereochemistry.



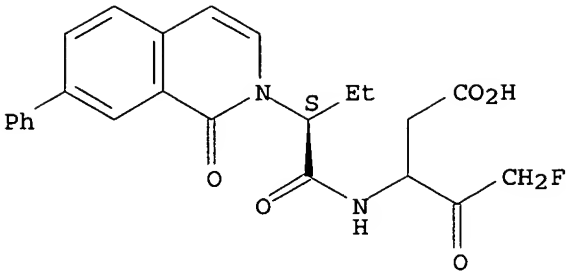
CM 2

CRN 76-05-1
CMF C2 H F3 O2



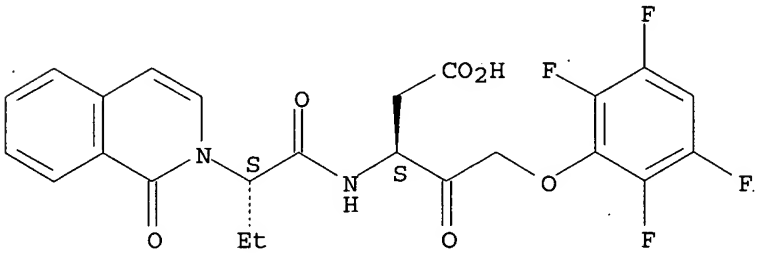
RN 618460-11-0 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-7-phenyl-2(1H)-isoquinolinyl)butyl]amino]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 618460-12-1 USPATFULL
CN Pentanoic acid, 4-oxo-3-[[(2S)-1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)butyl]amino]-5-(2,3,5,6-tetrafluorophenoxy)-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L19 ANSWER 10 OF 10 USPATFULL on STN
ACCESSION NUMBER: 2004:25175 USPATFULL
TITLE: Caspase inhibitor prodrugs
INVENTOR(S): Mortimore, Michael, Burford, UNITED KINGDOM
Golec, Julian M.C., Swindon, UNITED KINGDOM

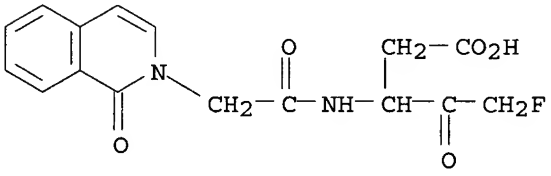
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004019017	A1	20040129
APPLICATION INFO.:	US 2003-366192	A1	20030211 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-355889P	20020211 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: FISH & NEAVE, 1251 AVENUE OF THE AMERICAS, 50TH FLOOR, NEW YORK, NY, 10020-1105
NUMBER OF CLAIMS: 22
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 206 Drawing Page(s)
LINE COUNT: 838
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to compounds of formula I which are prodrugs of caspase inhibitors and pharmaceutically acceptable salts thereof. This invention further relates to the release of caspase inhibitors from these compounds through selective bond cleavage. This invention further relates to pharmaceutical compositions comprising these compounds, which are particularly well-suited for treatment of caspase-mediated diseases, including inflammatory and degenerative

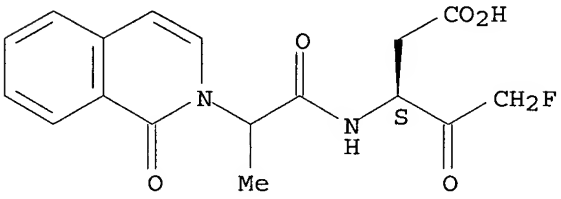
diseases. This invention further relates to methods for preparing compounds of this invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **344461-02-5 582317-55-3**
(phospholipids as caspase inhibitor prodrugs)
RN 344461-02-5 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[(1-oxo-2(1H)-isoquinolinyl)acetyl]amino]- (9CI) (CA INDEX NAME)



RN 582317-55-3 USPATFULL
CN Pentanoic acid, 5-fluoro-4-oxo-3-[[1-oxo-2-(1-oxo-2(1H)-isoquinolinyl)propyl]amino]-, (3S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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